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SYSTEMIC LUPUS ERYTHEMATOSUS: A COMPLEX AUTO-IMMUNE DISORDER? * †

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INTRODUCTION

SYSTEMIC (disseminated) lupus erythematosus has been known for at least 50 years, but its exact nature and the pathogenetic mechanisms bringing it about are almost as obscure now as they were when the disease was first described. Considered a rarity for the first three decades of the present century, its incidence seems to be increasing steadily, although whether this is actually so or the result of better recognition is difficult to state.

Systemic lupus must still be classed as a complex disorder of obscure origin. Even its histopathology has been in doubt, often in the hands of the same observers. Thus, Baehr, Klemperer and Schifrin in 1935 [1] concluded that the disorder was fundamentally one of small blood vessels, and pointed to the possibly specific nature of the "wire-loop" lesions in the glomeruli. In 1941, however, Klemperer, Pollack and Baehr [2] emphasized that it was not the blood vessels so much as the "ground substance" or collagen which was involved. This led to the present interpretation of lupus as a "collagen" disease.[3]

My own interest in this disorder, dating back some 30 years, was stimulated by the common findings of splenomegaly and leukopenia, and in some instances of hemolytic anemia or of thrombocytopenia. As knowledge of the histopathologic lesions developed, it was evident that some apparently

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typical examples of "idiopathic" thrombocytopenic purpura (ITP) showed the "onion-skin" vascular lesions of lupus in the small blood vessels of the removed spleen.[4] With the development of the Coombs' test as an indicator of antibody-globulin on the surface of the red blood cell, it also became apparent that some cases of systemic lupus showed a positive Coombs' test. Was this coincidental, was it "symptomatic" of the underlying disorder, or did it indicate that an immunologic disorder involving the red cells might be part and parcel of the disorder known as S.L.E.? Hargraves' [5] epochal observation of the "L.E. cell," which led directly to the discovery that the serum of patients with the disease possessed the "L.E. factor," [6] seemed to indicate that a serologic or immunologic disturbance at least affecting the leukocytes was present. In retrospect, this finding may be said to have begun the shift away from the purely histologic description of the disease to the more dynamic, immunologic approach we propose to follow below.

A number of observers have already indicated their belief that S.L.E. represents a hypersensitivity state, an allergic condition involving small blood vessels, or an immunologic disorder.[1, 6, 42, 43] It is our contention, as developed from analysis of our case material, that the disorder is a complex "auto-immune" condition involving not one set of tissues but fundamentally two, i.e., (1) the complex of mesenchymal tissues involved in small blood and endothelial surfaces, and (2) various constituents of the blood. That abnormal antibodies directed against specific cells of blood and marrow are probably responsible for such disorders as acquired hemolytic anemia with positive Coombs' test (auto-immune hemolytic anemia), idiopathic thrombocytopenic purpura, and certain cases of leukopenia, granulocytopenia and pancytopenia, has gradually assumed increasing recognition. We have also broached the possibility that certain disorders involving small blood vessels, such as thrombohemolytic thrombocytopenic purpura, and acute vascular (Henoch-Schönlein) purpura, might be auto-immune in nature.[19b, 33]

It must be conceded at the outset that the relatively new concept of "auto-immunization" rests on somewhat shaky foundations, since little if any experimental evidence for *auto-* as opposed to *hetero-* or *iso-*immunization has been established. Nevertheless, the fact that certain disorders involving red cells, white cells, platelets and some coagulation factors appear to be due to factors produced within the patient's own body, added to the fact that some of these factors, when studied by immunologic and other methods, have all the characteristics of immune antibodies, indicates rather strongly that an immunologic process is present. Since this develops within the patient's own body, it seems permissible to define the process as one of *auto-*immunization.

In the present paper, a number of cases of S.L.E. will be presented that emphasize the occurrence of various hematologic abnormalities of an "auto-immune" type. The L.E. factor will be discussed as one of the immunologic abnormalities of the disease. Finally, a consideration of systemic lupus as

a complex of auto-immune abnormalities involving various constituents of the blood and endothelial surfaces will be presented, together with some speculations as to possible mechanisms which might initiate or enhance the immunologic process.

Case Reports

A. S.L.E. with Thrombocytopenic Purpura ("ITP").

Case 1. This patient, now aged 29, developed her menarche at age 14; the menstrual flow was normal. At the age of 19 she first developed large ecchymoses with slight trauma and had spontaneous nosebleeds and slight bleeding from the gums. The menses became very profuse. In July, 1946, at the age of 19, although she appeared healthy, she showed numerous small ecchymoses, and petechiae were present both in the skin and in the buccal mucosa and the conjunctivae. The remainder of the examination was negative. The blood counts revealed: hemoglobin, 8.1 gm.; red blood cells, 4.16 million; white blood cells, 5,850, with polynuclears 72%; platelets, 0 (!). A sternal marrow puncture revealed a somewhat hypercellular marrow; megakaryocytes were abundant, but platelet production appeared to be nil. The diagnosis of ITP was made, and splenectomy was performed on July 13, 1946. The platelet count rose rapidly to high values. On August 7 the blood values were as follows: hemoglobin, 12.1 gm.; red blood cells, 4.22 million; platelets, 1.69 million; white blood cells, 9,200.

Somewhat later, during the summer of 1946 and following exposure to the sun at a beach, the patient developed a small reddish nodule just below the left eye on the upper cheek. Other nodules gradually developed in the course of the next nine years, eventually giving the typical appearance of the "butterfly" eruption of lupus erythematosus. In May, 1956, the patient complained of fatigue and the unsightly rash of the face. Physical examination revealed no abnormalities other than the "discoid" eruption of lupus. The blood counts revealed: hemoglobin, 11.2 gm.; red blood cells, 3.65 million; white blood cells, 6,500, with a normal differential count; platelets, 886,000. The L.E. preparation was negative. The urine showed no abnormalities.

Prednisone (Meticorten) in a dosage of 30 mg. daily was administered for one week beginning May 14, following which 20 mg. were given. The rash began to subside a few days after administration of prednisone was begun, and by May 29 had almost completely disappeared. Large, dilated, telangiectatic vessels were present at the sites of the previous eruption. The dosage of prednisone was reduced to 10 mg. daily, and, in addition, hydrocortisone ointment was prescribed locally. At this time, slight cervical and axillary lymphadenopathy was detected. Another L.E. test in July, 1956, was strongly positive. In October, 1956, the patient complained of pains in the shoulders and scapulae. No abnormalities of the joints were discovered. At the present time the patient is taking prednisone in a dosage of 5 mg. per day and using hydrocortisone ointment applied locally to the face. On this regimen she appears to be in excellent health, and the only remnant of the lupus eruption of the face is indicated by the presence of telangiectatic blood vessels on the upper cheeks and bridge of the nose.

*Case 2.** This patient was plagued with severe acne during her adolescence and was treated with various ointments and lotions and eventually given x-ray therapy to the face in September, 1950. In June, 1951 (age 20), there were pain, stiffness and limitation in motion of the finger joints. In September, 1951, spontaneous bleeding took place from the gums, and numerous ecchymoses of the extremities were

* This case has been previously reported.[7]

present following slight trauma. At one time a short bout of fever occurred, with a temperature rise to 103° F. In October, 1951, the patient looked well. A few petechiae of the gums and mucous membranes were present. Neither the liver nor the spleen was felt. There was no peripheral lymphadenopathy. A few finger joints showed questionable spindling. Numerous small ecchymoses of the thighs and upper extremities were present, together with a few petechiae of the lower extremities and below the clavicles. No eruption was present other than the scars of the previous acne. The blood showed moderate thrombocytopenia. Sternal marrow aspiration revealed normal cellularity, granulocytic hyperplasia and numerous megakaryocytes, with diminished platelet production. An L.E. test was negative. Therapy with ACTH and later with cortisone was only partially effective.

In December, 1951, the blood showed: hemoglobin, 10.1 gm.; red blood cells, 3.54 million; white blood cells, 12,400; platelets, 25,000; reticulocytes, 2.6%. The sedimentation rate was 116 mm./hr. Marked thrombocytopenia persisted, and on March 3, 1952, splenectomy was performed following resumption of cortisone (200 mg. daily) and the transfusion of two units of plastic bag blood. The spleen weighed 185 gm. and showed the typical vascular and perivascular "onion-skin" lesions of systemic lupus. The platelet count rose rapidly to levels of 1,000,000 and over. The Coombs' and L.E. tests were negative. Heterophil agglutination test was positive to a dilution of 1:112. Again, therapy with ACTH and later cortisone was instituted, with a partial therapeutic result, but when cortisone was discontinued relapse occurred. Pains in hands and wrists developed.

Four months after splenectomy the patient developed fever and interscapular and upper sternal pleuritic pain. She appeared to be acutely ill. A faint, diffuse macular rash was present over the abdomen and lower chest. Several small lymph nodes were present in the left axilla. There was a distinct pericardial friction rub, and at the left base fine râles were heard. The blood counts were essentially normal, but the sedimentation rate was 110 mm./hr. The urinary sediment disclosed small numbers of red cells and leukocytes. The L.E. test was now positive. Therapy with cortisone (300 mg. daily) was instituted. In one week the temperature returned to normal, the sedimentation rate was considerably reduced, and the indications of pericarditis, both clinically and by electrocardiogram, had disappeared. The dosage of cortisone was reduced gradually to 25 mg. daily, and eventually the drug was discontinued.

The patient remained well for about one year but then developed increasing fever. The signs of pericarditis again became evident, and the indications of renal disease became more marked. She became increasingly ill and died in April, 1954, two years following splenectomy.

Comment: This patient, after considerable chemical and x-ray therapy for acne, developed arthralgias at the age of 19 and shortly thereafter the typical features of ITP. The L.E. test was negative. Splenectomy resulted in a complete response on the part of the blood platelets. The spleen showed the typical vascular lesions of lupus. Four months later the various features of systemic lupus were present, responding at first to ACTH and cortisone therapy. The possibility is present that removal of the spleen was at least partly responsible for dissemination of the lupus process. The patient died approximately two years after splenectomy.

Case 3. This 22 year old married woman was admitted to the New England Center Hospital in July, 1954, because of severe thrombocytopenic purpura. Since childhood, epistaxes had been present, and since menarche, severe menorrhagia. In

October, 1953, there was easy bruising of the skin. In November, pregnancy was diagnosed. Severe epistaxes took place in February, and in June, 1954, vaginal bleeding and epistaxes led to the use of transfusions. On July 1, 1954, she passed a dead fetus, and her condition became desperate. The blood platelet count was 10,000 per cubic millimeter. Bone marrow examination disclosed numerous megakaryocytes without evident platelet production. The L.E. test was negative. ACTH and later cortisone were given, together with three transfusions of blood. There was a partial response. Splenectomy was performed on July 27, 1954, with a rapid rise in platelets. The splenic histology showed the typical features of lupus. The patient has remained well to the present time.

Comment: In this case of S.L.E. the various features of the disease, including the L.E. test, were completely lacking, the diagnosis being made from the characteristic "onion-skin" lesions in the spleen, which was removed because of the typical features of ITP. Was this case one of ITP with coincidental L.E. lesions of the spleen, or was the ITP a prodrome of L.E., i.e., one of the early features of the complex disorder known as S.L.E.? These matters will be discussed below.

Case 4. This woman novelist developed unusual fatigue in 1942 at the age of 46. Shortly thereafter the typical features of rheumatoid arthritis appeared, and an irregular eruption of the face was noted. In 1947 she developed severe menorrhagia, for which hysterectomy was performed. Later, spontaneous bruising and bleeding from mucous membranes led to the performance of blood examinations, and thrombocytopenia was discovered. On November 20, 1947, the spleen was removed, but there was little change in the platelet count or in the hemorrhagic state. The platelets varied between 40,000 and 80,000 per cubic millimeter. In 1948 the arthritis became severe and disabling, with involvement of fingers, wrists, elbows and knees. The platelet count in 1948 fluctuated between 130,000 and 275,000. The typical "butterfly" lesions of disseminated lupus were present. During the next few years both the arthritis and the lesions of lupus varied greatly from time to time. In 1951 there was slight generalized lymphadenopathy; the sedimentation rate was 80 mm./hr. In 1952 the lesions of lupus extended to the scalp. The L.E. test was positive, the Coombs' test negative, the serologic test for syphilis negative. Treatment with ACTH resulted in a striking improvement in the lupus and in the arthritis, and in a rise of the platelets to 400,000. From that time on the platelet count was consistently normal. In June, 1956, there was weight loss, and the joint pains were worse. In April, 1957, the lupus lesions had extended to the palms and fingers. However, the patient's general health was relatively good, and she was able to work regularly at her novel writing. In July, 1957, she died suddenly of subarachnoid hemorrhage.

Comment: Rheumatoid arthritis of moderate severity was the patient's first manifestation of her disease, and this was followed by a rash characteristic of discoid lupus. Five years later the characteristic features of ITP were present, but hysterectomy (for menorrhagia) and, later, splenectomy were without effect. ACTH and later the corticosteroids resulted in excellent remissions, particularly in the platelet count, which remained normal for five years. The lesions of discoid lupus gradually became disseminated, although the patient's general condition was reasonably good. She died suddenly of cerebral hemorrhage about five years after the beginning of her illness.

B. S.L.E. WITH AUTO-IMMUNE HEMOLYTIC ANEMIA.

*Case 5.** This 35 year old woman was first admitted to the New England Center Hospital on April 17, 1951, because of severe anemia. In October, 1950, she noted fatigue, pallor and painful joints, with slight swelling of the finger joints. Anorexia, mild fever and syncopal spells had also occurred. At hospitalization the patient was acutely ill, with a temperature of 105° F. There were marked pallor and slight icterus. The blood showed: hemoglobin, 3.4 gm.; red blood cells, 1,000,000; reticulocytes, 17%; white blood cells, 13,000. The red cells showed marked spherocytosis and polychromatophilia; five nucleated red cells were seen in counting 100 white blood cells. The sedimentation rate was 147 mm./hr. The osmotic fragility was increased, with hemolysis beginning at 0.6% (sodium chloride solution). The bone marrow showed striking erythroblastic hyperplasia. Several L.E. tests were negative. The direct Coombs' test was positive, and free auto-agglutinins and iso-agglutinins were detected at 37°, 20° and 3° C. The heterophil agglutination and the serologic tests for syphilis were positive, the former in a dilution of 1:112.

The patient responded well to transfusions and ACTH therapy. Normal blood counts were maintained during the second half of 1951, all of 1952, and the beginning of 1953, with cortisone in a dosage of 25 to 50 mg. daily. Splenectomy was performed on March 14, 1953, chiefly at the patient's insistence, because her face was "too round." The spleen weighed 180 gm., but the early "inflammatory" vascular lesions of lupus were noted. Hematologically the patient made an excellent recovery; the hemoglobin rose from 10 gm., reticulocytes dropped from 8% to 1.5%. In June, 1953, approximately two and a half months after splenectomy, the patient developed a facial eruption, then fatigue, fever, anorexia, weight loss and multiple joint pains. On June 16, 1953, the typical "butterfly" eruption of lupus was present, and slight spindling of finger joints was noted. The L.E. tests were now positive. Treatment with cortisone was instituted, with subsidence of all systemic manifestations. However, early in 1955 the typical lesions of "discoid" lupus† were present on the face and scalp, with extension to the back and arms. Treatment with chloroquine diphosphate seemed to improve the eruption. At the most recent visits the L.E. test continued to be positive; there were no systemic manifestations, and only a mild anemia without evidence of increased hemolysis was present. The patient is now taking 0.25 gm. of chloroquine diphosphate daily.

Comment: This patient with the typical features of auto-immune hemolytic anemia also showed arthralgias, slight lymphadenopathy, and, in addition, a positive Coombs' test, a positive heterophil agglutination test, and positive serologic tests for syphilis. The L.E. tests were consistently negative until two and a half months after splenectomy, when the patient developed various manifestations of systemic lupus. On corticosteroid therapy the systemic symptoms were kept in check, but the lesions of "dis-

* This case has been previously reported by us.[7]

† There is increasing indication that so-called discoid cutaneous lupus and systemic lupus are probably variants of the same generalized disease.[8] Careful follow-up of the chronic discoid cases indicates that, with the years, various features of systemic lupus may develop: rheumatoid arthritis, nephritis, splenomegaly, thrombocytopenic purpura, etc. The only difference between the two conditions is probably that of degree or of rapidity of course. The discoid type may be thought of as a "stretched-out" acute or disseminated type; similar abnormalities develop, but in a "slow motion" fashion. The acute or disseminated form may be thought of as a highly "concentrated" condition, in which many abnormalities occur within a short space of time; the chronic form is more indolent. "Transitional" types are not infrequently seen.

coid" lupus developed when cortisone was discontinued. It seems likely that splenectomy led to dissemination of the lupus process.

*Case 6.** This 53 year old woman was first admitted to the New England Center Hospital on November 11, 1952, complaining of fatigue and anemia. In 1936 pelvic tuberculosis had been discovered. Later, following a pelvic operation, the patient developed a chronically draining abscess and was treated for pelvic and bone tuberculosis for four years. For about one year she had noted that exposure to sunlight seemed to precipitate arthralgias of the hands, feet and ankles. Upon admission to the hospital in 1952 she showed severe anemia: hemoglobin, 4.8 gm.; red blood cells, 1.45 million; hematocrit, 18%; reticulocytes, 25%; a moderate reduction in platelets to 160,000; a normal white count (7,200); and a very rapid sedimentation rate (152 mm./hr.). The urine showed a trace of albumin. The Coombs' test was positive, and free iso-antibodies and auto-antibodies were present at 37°, 22° and 3° C. L.E. tests were negative.

Therapy with ACTH was at first instituted, with a striking rise in red cell count and platelets, and a reduction in reticulocytes. Splenectomy was performed on December 2, 1952, because of the possible danger of continued corticosteroid therapy in a woman with previous tuberculous disease. The spleen, which weighed 190 gm., showed vascular changes consistent with lupus. Complete remission in all the patient's symptoms followed, but about five months later (May, 1953), arthralgias and a skin eruption on the exposed surfaces of the body developed. In September, 1953, the L.E. test was positive for the first time. In February, 1954, marked anorexia, weight loss, rash, fever, chest pain, generalized lymphadenopathy and extreme wasting developed. The hemoglobin level showed a moderate drop, with associated reticulocytosis. The L.E. tests were positive, the urine showed a trace of albumin, the sedimentation rate was 71 mm./hr., and the Coombs' test was positive. The patient was given cortisone "covered" with para-aminosalicylic acid and streptomycin. There was gradual improvement in all the symptoms, signs and blood counts; since then, the patient has continued in good health, taking daily maintenance doses of 25 mg. cortisone and, more recently, prednisone, 5 to 10 mg.

Comment: This patient, with previous chronic pelvic and bone tuberculosis, had arthralgias and a mild skin eruption of the face following exposure to the sun about a year prior to the development of severe auto-immune hemolytic anemia and mild thrombocytopenia. The L.E. tests were negative. Splenectomy, which revealed the vascular lesions of lupus, was followed in five months by a skin eruption and arthralgias, and in a year by most of the various manifestations of systemic lupus, including a positive L.E. test. Therapy with corticosteroids resulted in a striking remission, which continues to be maintained. It is possible that splenectomy was at least partly responsible for dissemination of the lupus process.

Case 7. In July, 1955, this 17 year old girl was admitted to the New England Center Hospital. During the previous three years she had developed arthralgias with increasing stiffness of the joints, a "butterfly" eruption of the face, Raynaud's phenomenon, and intermittent fever. Upon admission to the hospital there was moderate pallor without icterus. The "butterfly" eruption was not seen, but there was definite vascularity of the cheeks and nose. The heart showed a Grade II systolic murmur over the apex. Both the liver and spleen were felt about 3 cm. below

* This case was previously reported elsewhere.[7]

their respective costal margins. Fusiform swellings of the finger joints were present, with the spindling deformities of early rheumatoid arthritis. The skin of the fingertips was slightly atrophic, with marked discoloration due to large, irregular blood vessels. The blood counts showed: hemoglobin, 8.0 gm.; red blood cells, 2.75 million; hematocrit, 29%; white blood cells, 7,700, with polynuclears 70%; reticulocytes, 7.4%. Polychromatophilia was increased, and there was slight spherocytosis. The Coombs' test and the L.E. test were positive; the serologic tests for syphilis were negative. The diagnosis of S.L.E. with an auto-immune hemolytic component was made. Prednisone was begun in a dosage of 60 mg. daily, and then gradually reduced. There was immediate improvement in all symptoms, although fatigue persisted. The hemoglobin level and the red cell count rose to normal values. Gradually the dose of prednisone was reduced to 15 mg. daily.

In September, 1956, dull supra-orbital headaches were very disturbing, and a severe "fainting" spell took place. The hemoglobin was 9.6 gm.; red blood cells, 3.4 million; white blood cells, 4,100, with 80% polymorphonuclears and 7.8% reticulocytes. The Coombs' test was positive. The sedimentation rate was 13 mm./hr. The red cells were hypochromic and microcytic. The serum iron was 60 μg.%, and the possibility of a concomitant iron deficiency state was raised. Iron was given, and a rise in hemoglobin and red cell count took place. Since then the patient has been taking small doses of prednisone (5 mg. daily for maintenance) and has been feeling well except for vasomotor changes with cold weather. Although the blood counts have been normal (hemoglobin, 12 to 12.5 gm.), the Coombs' test has continued to be positive.

Comment: This girl of 17, with various manifestations of lupus, developed auto-immune hemolytic anemia in the course of her illness; complete remission in all the manifestations occurred with prednisone therapy.

C. S.L.E. with Auto-Immune Hemolytic Anemia and ITP ("Evans' Syndrome").

Case 8. This 10 year old girl was admitted to the New England Center Hospital on September 8, 1954, because of anemia. Menarche had been established a few months previously, and there was severe menorrhagia. In June, 1954, numerous ecchymoses appeared, followed by severe epistaxes and hematemeses. The diagnosis of ITP was made and the patient treated with cortisone. Upon admission to the New England Center Hospital, striking pallor was noted, together with slight icterus, hepatomegaly and splenomegaly, and numerous ecchymoses and petechiae. The blood showed: hemoglobin, 2.7 gm.; red blood cells, 900,000; white blood cells, 15,000; platelets, 87,000; reticulocytes, 39.4%. The Coombs' test was positive, the L.E. test negative; the serologic tests for syphilis were positive. The bone marrow aspiration showed a striking erythroblastic hyperplasia; megakaryocytes were numerous but without obvious platelet production. The diagnosis of combined ITP and auto-immune hemolytic anemia (Evans' syndrome) was made, and the possibility of systemic lupus was seriously considered in view of the combined hemolytic and thrombocytopenic disturbance, and the finding of a positive serologic test for syphilis. Therapy with cortisone was instituted, and the steroid was given continuously for almost a year. At the end of that time (July, 1955), when the blood counts were completely normal, cortisone was discontinued. A few months later there was a slight drop in red cell count and a slight rise in reticulocytes. In December, 1955, the patient complained of painful knee and ankle joints. The hemoglobin had again dropped slightly. In January, 1956, the L.E. test was strongly positive for the first time; the knee and ankle joints were painful; the spleen was again enlarged. Therapy

with Meticorten (45 mg. daily) was instituted, but erythema and itching of hands and feet developed; on cortisone, these symptoms were relieved. At the present time the patient is in excellent health clinically and has normal blood counts. However, the Coombs, L.E. and serologic tests for syphilis continue to be positive.

Comment: In this girl of 10, thrombocytopenic purpura was the first manifestation of disease, and was promptly followed by severe auto-immune hemolytic anemia, effectively treated with cortisone. Later, when cortisone was discontinued, joint pains appeared and the L.E. test became positive. Continued therapy with cortisone was followed by complete clinical and hematologic remission, but the Coombs', L.E., and Hinton and Kahn tests retained their positivity.

Case 9. This 24 year old married woman had been well until the age of 21, when she developed menorrhagia and numerous ecchymoses. She was found to have the following blood counts: hemoglobin, 62 gm.%; hematocrit, 28%; white blood cells, 3,300, with 67% polymorphonuclears; platelets, 60,000. Therapy with ACTH was followed by improvement, but when prednisone in a dosage of 10 mg. daily for maintenance was given the platelets again dropped to 60,000. Splenectomy was then performed (February, 1955). There was a stormy postoperative course, with "atelectatic" pneumonia, pain in the right lower extremity, inguinal lymphadenopathy, anemia, and continued thrombocytopenia. The splenic histology disclosed the typical features of lupus, but two L.E. tests were negative. Therapy with cortisone was moderately effective in controlling the clinical and hematologic manifestations. In November, 1955, corticosteroids were discontinued. This was followed one month later by the development of generalized lymphadenopathy, and later by progressive anemia. Multiple joint pains, chest pains on inspiration, anemia and fever developed and became progressively worse. Therapy with prednisone in a dosage of 10 to 15 mg./day was without effect. The anemia became more marked, and in July, before transfer to the New England Center Hospital, the hemoglobin was 5.3 gm., the hematocrit 19%. Transfusion had not been given because of the difficulty of "cross-matching" the patient's serum against numerous donor red cells.

Examination revealed marked pallor, slight icterus, slight generalized lymphadenopathy, a loud, blowing systolic murmur over the entire precordium, and a presystolic gallop rhythm. The blood showed: hemoglobin, 3.9 gm.; hematocrit, 14%; red blood cells, 1.21 million; white blood cells, 18,500, with 53% polymorphonuclears and 5% mononuclears. Two hundred thirty nucleated red cells were seen in counting 100 white cells! There was marked spherocytosis. The reticulocytes numbered 62%! The extraordinary erythroblastosis and reticulocytosis were interpreted as part of the reaction of regeneration in a splenectomized individual with continued hemolytic anemia.

The serum bilirubin was 1.9 mg.%. Bone marrow aspiration revealed an extraordinary erythroblastic proliferation with many mitoses. Several L.E. tests were consistently negative. The Coombs' test was positive. The serum showed a strong cold hemagglutinin.

The patient was given two units of warm, washed, group O, Rh negative red cells; following the second unit a mild reaction took place, with chills and fever. Meticorten therapy was instituted in a dosage of 100 mg. daily, with quick clinical and hematologic improvement. The patient was discharged on August 1, still taking Meticorten, 100 mg. daily. On August 9 the blood findings were: hemoglobin, 11.9 gm.; red blood cells, 3.62 million; white blood cells, 10,500; platelets, 448,000; reticulocytes, 3.2%. There was continued improvement, with the hemoglobin on

September 17 rising to 14.6 gm.; red blood cells were 4.69 million; platelets, 765,000. The prednisone was gradually reduced to 10 mg. daily, but two months after this dose was attained the patient developed fever, vomiting and a "butterfly" eruption of the face, together with a reduction in hemoglobin, red cell and platelet values. When the dose of prednisone was raised to 15 mg. daily the patient developed an excellent clinical and hematologic remission. After many negative tests with various technics the L.E. test was eventually found to be positive in July, 1957.

Comment: This young woman first developed the typical features of ITP, for which splenectomy was done. This showed the characteristic vascular lesions of lupus, although the L.E. tests were negative. Cortisone was used for about a year to control various systemic symptoms that developed after splenectomy, but when this was discontinued severe auto-immune hemolytic anemia developed. On large doses of corticosteroids there was complete clinical and hematologic response, but when too small a dose of prednisone was given relapse occurred, including a "butterfly" eruption. It is noteworthy that the L.E. test was consistently negative for more than two years in the face of every other manifestation of the systemic disease.

D. S.L.E. WITH POSITIVE SEROLOGIC TEST FOR SYPHILIS AND MARKED LEUKOPENIA AND NEUTROPENIA.

Case 10. This 39 year old unmarried woman was referred in 1950 for consideration of splenectomy because of possible "splenic neutropenia." In 1950 a positive test for syphilis was discovered when the patient volunteered as a blood donor. She stated that she had never had sexual intercourse (examination revealed an intact hymen), and disclaimed sores or other evidence of syphilis. She was nevertheless treated with large doses of penicillin. In February, 1951, she suddenly developed a "badly swollen" eye. In August there were multiple severe arthralgias. After exposure to the sun she developed what was considered to be "cellulitis" of one eye. During 1952 the finger joints were painful and often swollen. The patient traveled a good deal because of her occupation as an insurance executive. During one of her trips a physician again found a positive test for syphilis, and again therapy with massive doses of penicillin was given. In March, 1954, bouts of low grade fever developed. Hospitalization revealed leukopenia (white blood cells, 3,500). In May, 1954, painful swelling of ankle and knee joints occurred. In August, 1954, fever recurred and was associated with migratory arthritis. In September while at a beach the patient again developed marked swelling and redness of the left eye, so severe as to result in hospitalization. She was febrile, had pain in the left chest with a pleural friction rub, and showed a white count which fluctuated between 1,300 and 2,300, with 5 to 25% granulocytes. The diagnosis of "relapsing neutropenia" was made.

When the patient was seen again in November, 1954, she was mildly asthenic and showed slight pallor. There was minimal lymphadenopathy. Questionable spindling of finger joints was present. There was no indication of a "butterfly" eruption. Neither the spleen nor the liver was palpable, and the remainder of the examination was negative. The blood counts were as follows: hemoglobin, 11.6 gm.; red blood cells, 3.71 million; white blood cells, 4,500 to 5,000; polymorphonuclears, 62%; platelets, 516,000. The sedimentation rate was 90 mm./hr., the Hinton and Kahn tests were positive, the Coombs' test was negative, the L.E. test positive. The patient was observed on only one further occasion, when the L.E. test was again positive.

Comment: The initial abnormality in this case was a positive serologic test for syphilis. Later, several attacks of "cellulitis" of the left eye took place on exposure to sunlight at the beach. Arthralgias and arthritis, pleuritis, bouts of fever, and severe leukopenia and neutropenia led to the diagnosis of "relapsing neutropenia," for which splenectomy was advised. Eventually the diagnosis of S.L.E. was made on the basis of the above manifestations, together with a positive L.E. test.

E. S.L.E. WITH A HEMORRHAGIC DISORDER DUE TO AN ANTICOAGULANT.

Case 11. This 29 year old married woman developed her menarche at the age of 13. Her periods from then on were characterized by profuse bleeding, lasting seven days and requiring the use of numerous double pads. At the age of 18, while she was working as a technician, a prolonged prothrombin time was discovered during a "control" test. Various hemorrhagic manifestations, including easy bruising with trauma, were present. At the age of 19 a positive serologic test for syphilis was discovered when the patient applied for a marriage license. Shortly after she was married exsanguinating menstrual periods took place, requiring her first transfusion. However, she then had three children in successive years (at ages 21, 22 and 23) without undue bleeding. Shortly after her third pregnancy, migratory polyarthritis developed. This was quite severe, involving chiefly the fingers. At the age of 25 sterilization was advised because of successive exsanguinating periods; this was done by radium implantation. Hysterectomy was thought inadvisable following the return of a clotting time determination of eight hours (!). It was apparent from her further course that an inflammatory radiologic reaction took place in the pelvis as the result of the radium implants. Continued vaginal bleeding presented a severe problem, requiring numerous transfusions. Eventually the patient was referred for further evaluation of the hemorrhagic condition, which had received various diagnoses (congenital hypoprothrombinemia, atypical hemophilia, etc.). At the New England Center Hospital (June 4, 1954), the patient was somewhat pale, with flushed cheeks. A few ecchymoses of the thighs and arms were present. There was no hepatomegaly, but the tip of the spleen was felt. No lymphadenopathy was present. The heart showed no abnormalities. Questionable "spindling" of the finger joints was present. Blood examination revealed: hemoglobin, 11.8 gm.; red blood cells, 3.89 million; white blood cells, 14,200, with 84% polymorphonuclears; platelets, 1,700,000. The sedimentation rate was 69 mm./hr. The Hinton and Kahn tests were positive. Study of the hemorrhagic tendency showed a greatly prolonged coagulation time both in glass and in silicone, a greatly prolonged prothrombin time (17% concentration), normal accelerator factors, normal fibrinogen, a marked reduction in antihemophilic globulin, and normal PTC and PTA factors. No circulating anticoagulants were found. An electrocardiogram disclosed "pericarditis." The serum total protein was 7.2 gm.—albumin, 3.4; globulin, 3.8 gm.; L.E. tests were negative.

X-rays of the urinary tract showed pyelonephritis and stricture of the right ureter. The urologist suggested regular dilatations of the ureter, which were begun at this admission and continued at regular intervals thereafter. Although the diagnosis of S.L.E. was thought likely in view of the arthralgias, the positive serologic test for syphilis, the rapid sedimentation rate, the hypergammaglobulinemia, the peculiar "double" hemorrhagic difficulty (hypoprothrombinemia, and anti-hemophilia globulin (AHG) deficiency), and the "electrocardiographic" pericarditis, no positive diagnosis was made, and the patient was discharged as an example of con-

genital hypoprothrombinemia and acquired deficiency of antihemophilia globulin. She was advised to take prednisone in a dosage of 12.5 mg. daily.

The patient was re-admitted to the hospital on February 24, 1956, for continued urinary difficulty. A grade II systolic murmur was heard over the apex. The spleen was no longer palpable. Blood examination: hemoglobin, 10.2 gm.; reticulocytes, 3.3%; platelets, 716,000; white blood cells, 3,000. The Coombs' test was negative, the sedimentation rate was 105 to 124 mm./hr. There were two new laboratory findings at this time: (1) a thromboplastin inhibitor (antithromboplastin), and a possible antiprothrombin; and (2) a strongly positive L.E. test.

The diagnosis of S.L.E. was now made, and therapy with prednisone was instituted in a dosage of 50 mg./day. Following less than two months of prednisone therapy the patient was studied again on April 12, 1956. At this time the sedimentation rate was normal, the clotting time in glass was reduced to normal, the prothrombin time was almost normal, and the anticoagulant factors previously present were no longer demonstrated. The patient's condition then steadily improved. The ureteral dilatations became progressively fewer in number. Maintenance therapy with 12.5 mg. of prednisone has been continued.

Comment: In this patient a hemorrhagic tendency had been evident since menarche, and was eventually traced to hypoprothrombinemia. A positive serologic test for syphilis, arthralgias, precordial systolic murmur, "electrocardiographic" pericarditis, high sedimentation rate and hyperglobulinemia were all suggestive of systemic lupus, although the L.E. test was negative. A hemorrhagic survey disclosed a double coagulation defect, namely, hypoprothrombinemia and AHG deficiency. Prednisone in small dosage was given for a brief period. Later, when circulating anticoagulants against thromboplastin and prothrombin were discovered and the L.E. test was positive, the diagnosis became obvious. Therapy with large doses of prednisone resulted in striking improvement in all the clinical and laboratory abnormalities.

Discussion

1. *Analysis of the Various Disorders Found In S.L.E.:* Systemic lupus must surely be considered a protean disorder. Originally, it seemed to be primarily and fundamentally a dermatologic disease. However, even from the time of Kaposi [9] in 1872, severe constitutional symptoms were described, and the occurrence of lymphadenopathy, anemia and joint manifestations was noted. In 1895 Osler [10] noted the development of various visceral manifestations, as well as arthritis and thrombocytopenic purpura in certain cases of "erythema exudativum multiforme." In 1904 Jadassohn [11] reëmphasized the frequency of constitutional symptoms, as well as involvement of joints and serous and mucous membranes. Libman and Sacks in 1924 [12] described two cases of S.L.E. with "nonbacterial endocarditis," and in 1935 Baehr, Klemperer and Schifrin [1] stressed the striking incidence in the disease of pericarditis, pleuritis and glomerulitis with "wire-loop" lesions. The terms "disseminated" and "systemic" for what seemed to be originally a dermatologic disease were certainly apt.

Emphasis on the hematologic abnormalities of lupus was somewhat slower in development. Gradually, however, it became apparent that leukopenia, thrombocytopenic purpura,[13] a positive Coombs' test with auto-immune hemolytic anemia,[14] combined hemolytic anemia with thrombocytopenia,[15] a false-positive serologic test for syphilis,[16] and even a hemorrhagic disorder due to "anticoagulants" [17] were frequently associated with the disease. These conditions were almost always interpreted as secondary or "symptomatic" manifestations or complications of the disease, rather than as integral features, like the dermatologic lesions or the histologic abnormalities. With the discovery of the "L.E. cell," [5] first in the bone marrow and later in the blood,[6] and eventually the demonstration that the serum of patients with S.L.E. contained a factor which acted upon leukocytes in such a manner as to induce nuclear phagocytosis,[18] a shift in emphasis from

TABLE 1

Systemic Lupus: A Complex of Two Sets of Auto-Immune Abnormalities

A. Endothelium—Small Blood Vessels	*B.* Blood
Joints	Red cells—auto-immune hemolytic anemia (Coombs' test)
Pleura	White cells—leukopenia (L.E. Factor)
Pericardium	Platelets—thrombocytopenic purpura (Platelet agglutinin)
Endocardium	Coagulation abnormalities
Glomeruli	"Hemophilia" (antithromboplastin)
Other small blood vessels	"Hypoprothrombinemia" (antiprothrombin)
Skin	"Syphilitic" antibody (Serologic test for syphilis)
Spleen, etc.	

the histologic to the more dynamic serologic approach may be said to have begun. This has eventually led to the thesis developed in the present discussion, namely, that systemic lupus—its clinical, hematologic and histologic features—is the end-result of a series of reactions, probably immunologic, directed against various endothelial and hematologic constituents.

An analysis of the various abnormalities found in the cases presented above leads one to the following conclusions: (a) that there is great variation in the degree and number of possible abnormalities from case to case and from time to time in the same case; and (b) that there are fundamentally two sets of abnormalities: (1) those relating to the small blood vessels or endothelial surface vasculitis, and (2) those relating to various constituents of the blood. These are listed in table 1.

Cases of S.L.E. vary greatly in both the number and the degree of the various abnormalities listed in table 1. Naturally, if one has the advantage of following a case for a number of years, the number of abnormalities usually increases. One may draw up, as a sort of minor game, a "score sheet" of the lesions found in a given case, based on the tabulation given

above. On this basis, case 1 of our series had a "score" of only 3½, whereas case 8, showing arthritis, lymphadenopathy, skin lesions, hemolytic anemia with positive Coombs' tests, ITP, and positive serology presented the high score of 11. It is possible, as noted in some of our cases, to begin with an "L.E. score" of only 1 (i.e., ITP), with the development of a larger score either rapidly or very slowly, according to the degree of acuteness or chronicity of the case in question (i.e., perhaps according to the severity of the immunologic abnormality).

Emphasizing the hematologic abnormalities of the disease, as we have done in this discussion, leads us to conclude that they are as much a part of systemic lupus as are the histologic features found in the skin, the kidneys and the heart. Stated differently, the hematologic abnormalities of lupus may be considered not as "symptomatic" or "secondary" manifestations, but as integral parts of the disease. According to this concept, S.L.E. is a condition in which there is involvement of both small blood vessels and blood. Any one of the various manifestations of blood or blood vessel involvement may be in the foreground at a given time, or may be the presenting symptom. Thus, in the cases presented above, the initial symptom varied from ITP to hemolytic anemia, from severe neutropenia to hemorrhagic disease or from arthritis to a positive serologic test for syphilis. Various so-called "cardinal" manifestations of this complex disorder may be lacking at a given time, perhaps because of the lack of immunologic "bombardment" of a particular target organ. Thus, some cases may not have the lupus abnormality of the skin, and others may have a negative L.E. test. On this account the diagnosis of lupus, although often difficult, can never be considered to be dull.

2. *Analysis of the Hematologic Abnormalities of S.L.E. as "Auto-immune" Reactions:* The hematologic abnormalities of the disease are more readily studied during life than are the histologic ones. With the technics presently available it is also possible to define their immunologic nature far better than is the case with the blood vessels and endothelial surfaces.

The positive Coombs' test seen not infrequently in S.L.E. and its association with hemolytic anemia [14] are identical with those found in "idiopathic" auto-immune hemolytic disease. From the numerous studies over the last 20 years made by ourselves and others,[15, 19] it is evident that the red blood cells in this condition are (a) coated with a globulin substance, apparently of immunologic type, thus giving a positive reaction with the Coombs' antiglobulin serum, and (b) rendered susceptible to injury and subsequent ready hemolysis, with resultant hemolytic anemia. The term "auto-immune" hemolytic anemia has gradually increased in favor as it has become apparent (1) that an immunologic process is present, and (2) that the process apparently arises within the individual himself. Although the exact mechanism by which the auto-immune process arises has not been demonstrated, either in the clinic or experimentally, it may be presumed

that the hemolytic anemia, of both the "idiopathic" type and that seen as a manifestation of S.L.E., has developed in response to some as yet obscure antigen, presumably an altered red blood cell. Whether simple alteration of red cells might conceivably render them antigenic within the milieu of certain individuals, or whether a "hapten" is required, is obscure at the present time, and in any event is beyond the scope of the present paper.

Evans et al. in 1951 [20] pointed to the occasional occurrence of cases of ITP in association with auto-immune hemolytic anemia. They suggested the term "immunothrombocytopenia" for ITP, and the many studies done since then have amply confirmed this viewpoint. Our studies [21] demonstrated a short survival time of platelets when transfused to patients with ITP, indicating an extrinsic destructive mechanism, similar to that which involves the red cells in auto-immune hemolytic disease. Harrington and co-workers [22] demonstrated a "thrombocytopenic factor" in the plasma of cases of ITP by injecting large amounts of ITP plasma into normal individuals, who then developed thrombocytopenia. Other studies have shown the immunologic nature of this thrombocytopenic factor, which is evidently an agglutinin.[23] Because the platelet is a more difficult cellular material to work with than is the red cell, a reliable test for platelet antibody adherent to the platelet surface, as with the Coombs' antiglobulin test, has not yet been developed, and the interpretation of positive tests for platelet agglutination has been difficult.[24] Nevertheless, there are so many parallels between ITP and auto-immune hemolytic disease, and so much evidence for an immunologic abnormality in ITP, that it is highly probable that most cases of ITP are on an auto-immune basis.

Again, the mode of development of an immunologic reaction in patients eventually developing ITP is not known. However, from studies with Sedormid [25] and quinidine [26] thrombocytopenia, it is apparent that these substances, among other chemicals, may act as haptens, rendering platelets antigenic and producing highly specific platelet antibodies, which react only in the presence of the drugs in question. Antigenicity of platelets in ITP may conceivably be initiated either through physical alterations of platelets or through the attachment of haptens of various sorts, thus rendering the platelets "unrecognized" by antibody-producing tissues and therefore antigenic. Since the thrombocytopenic purpura of S.L.E. is identical in every respect with ITP, and since apparently typical ITP may be simply an early manifestation (prodrome) of lupus, it is possible that both "idiopathic" thrombocytopenia and the thrombocytopenia of S.L.E. are based on abnormal immunologic reactions.

That ITP and systemic lupus are closely related becomes increasingly evident as more and more cases are studied and followed. Apparently typical cases of ITP, showing no indications of systemic disease, may show the vascular lesions of lupus at splenectomy. Furthermore, following operation, such manifestations of S.L.E. as fever, pericarditis, pleuritis, "butter-

fly" facial eruption, etc., may develop either within a few months or gradually over the period of a year or more.[7] Whether these indications would develop in a given case without splenectomy, or whether they could be accelerated or even somehow induced by the operation, are legitimate subjects for speculation. There can be no question that severe thrombocytopenia, identical in all its features with ITP, may arise at some time during the course of S.L.E. and without reference to splenectomy. In some cases the thrombocytopenia is associated with auto-immune hemolytic anemia, giving the "double" condition which we have referred to as Evans' syndrome.[19b] Thus ITP, as stated above, may be considered as one of the several auto-immune processes making up the complex disorder we know as S.L.E. As a corollary to Evans' statement, when ITP occurs in a young woman it must be considered as a possible prodrome of the more serious S.L.E.

Since the strong possibility of dissemination of the lupus process following splenectomy is present, it is probably best to postpone splenectomy as long as possible. The various recent studies in ITP indicate that it probably represents a self-perpetuating immunologic mechanism which, once set up, is difficult to modify; splenectomy, if done, may represent simply an incident in the course of the disease, and may result in the exacerbation of a previously latent lupus process. The high relapse rate following splenectomy, together with the beneficial effects of the steroid hormones, notably prednisone, in raising the platelet count and producing remissions, has acted as a deterrent in our clinic to the routine recommendation of splenectomy. Thus, in the last two years we have refrained as far as possible from performing splenectomy, hoping in a few years to amass data as to its value or possible harm.[27] A curious feature of our case material is that systemic lupus has developed only in splenectomized women; none of our male patients splenectomized for ITP has thus far shown any of the manifestations of S.L.E.*

Leukopenia is a common characteristic of S.L.E. In some cases, as noted above, the leukopenia and neutropenia may be very severe, in some instances at levels close to those seen in agranulocytosis. This disorder and, more recently, some cases of severe neutropenia have been ascribed to the development of an abnormal immunologic mechanism directed against the leukocyte.[29] In S.L.E. a peculiar serologic abnormality, namely, the L.E. factor, has been found and has assumed the status of a specific and pathognomonic test. The L.E. factor is evidently a substance which has the capacity to react specifically with the nuclei of leukocytes. Against both the patient's leukocytes and those of normal individuals, this serologic factor eventually brings about the phagocytosis of nuclei or parts of nuclei.[16, 43] It is also possible that it is concerned in the development of leukopenia, although it is conceivable that other antileukocytic factors may be present.

* A preliminary survey of 51 consecutive cases of "typical" ITP splenectomized since 1949 indicates that 15.7% were eventually found to have systemic lupus; another 15% showed several manifestations of lupus, but the diagnosis could not be made positively.

Thus, leuko-agglutinins [29] and leukoprecipitins [30] have recently been described. We assume, as others already have done, that the L.E. factor indicates a reaction of an auto-immune type against leukocytes.[43, 44]

A positive serologic test for syphilis in lupus has attracted attention for many years. Why complement fixation for beef heart antigen occurs in syphilis is not known, but that it indicates an immunologic response to the disease appears certain. Similarly, in S.L.E. the complement fixation test or the newer Kahn and Hinton tests may be positive in the presence of a negative test for *Treponema pallidum* immobilization.[31] It seems permissible to speculate that the positive serologic tests for syphilis found in S.L.E. represent another auto-immune reaction which may occur in the disease. The heterophil agglutination test, which is positive in some cases of lupus, may well be on a similar basis.

Finally, the most recently studied hematologic reaction in lupus is that of the severe hemorrhagic disease (or diseases) due to disturbances in the clotting mechanism induced by the presence of "anticoagulant" or inhibitor substances.[17] A case of this type, where both hypoprothrombinemia and a deficiency in antihemophilic globulin were present, is described above (case 11). Since the coagulation disorder in this and other cases was evidently due to the presence of anticoagulant factors, it is reasonable to speculate that this, too, is immunologic in variety (i.e., auto-immune "hemophilia" or "hypoprothrombinemia").

Thus there is evidence, from analysis of clinical, hematologic and immunologic abnormalities in the disease, that numerous abnormal immunologic mechanisms, i.e., versus red cells, white cells, platelets, the "antigen" of syphilis, and certain blood coagulation constituents, may occur. Since these immune reactions apparently arise within the individual's own body, and attack various constituents of his own blood, they may be considered "auto-immune," although their mode of origin has not as yet been demonstrated.

3. *S. L. E. as an Auto-immune Disorder of Complex Type:* We have shown how it is possible to conceive of the abnormal hematologic reactions seen in S.L.E. as auto-immune in type, and have also postulated that the hematologic reactions are as much an integral part of the disease as are the various abnormalities of small blood vessels and endothelial surfaces giving rise to the so-called characteristic lesions of lupus, i.e., the dermatitis, the renal abnormality, arthritis, etc. One may extend this argument further by assuming that the various blood vessel lesions are also auto-immune.

That "vasculitis" may be immunologic in origin has been discussed for some years. Experimental "hetero-immune" generalized vasculitis resembling the clinical and histologic lesions seen in Henoch-Schönlein vascular purpura has been produced by several groups of workers.[32] We have pointed out the generalized character of Henoch-Schönlein purpura and the possibility that the disease is of auto-immune variety;[33] Bernard and co-

workers have presented some evidence for this concept.[34] Some of the lesions seen in this disease are strikingly similar to those found in lupus. The vasculitis of several disorders, including the ulcerative lesions of chronic Henoch-Schönlein disease and of various ill-defined disorders, has been considered to be of immunologic or hypersensitive type by McCombs, Patterson and McMahon.[35] That the generalized vascular disturbance affecting larger blood vessels and known as periarteritis nodosa may be immunologic in nature has been postulated by several workers, and was put on a reasonably firm experimental basis by Rich.[36] Rheumatoid arthritis is considered by many to be immunologic in origin; the several immunologic tests that have been developed in recent years appear to support this viewpoint.[37] Acute glomerular nephritis, either as a single disorder or as occurring in the course of Henoch-Schönlein purpura, has also been considered to be of immunologic origin.[38] On this basis, it is conceivable that the various features of S.L.E. which are on the basis of vascular abnormalities are immunologic in origin, i.e., auto-immune. These would include the vasculitis causing the typical "butterfly" reaction, the arthritis identical with that of the "rheumatoid" variety, and the glomerulitis leading to chronic nephritis, as well as such other abnormalities as pericarditis, endocarditis, pleuritis, etc. The many histologic lesions of lupus could conceivably be due to a more or less generalized vasculitis of immunologic origin, involving a variable number of organs throughout the body to greater or less extent. Evidence for these speculations has thus far been difficult to obtain in view of the present lack of good technics for detecting vascular antibodies. This is quite in contrast with the relative simplicity of immunologic tests for blood cells and blood serum constituents.

If, to continue the argument further, one considers that both the hematologic and the vascular disturbances of lupus are auto-immune, the entire disorder may be considered as a complex of auto-immune vascular and hematologic abnormalities. Of the various "auto-immune" disorders that we have described as such (hemolytic anemia, ITP, Evans' syndrome, acute (Henoch-Schönlein) vasculitis, thrombohemolytic thrombocytopenic purpura, etc.),[15] lupus may be considered to be the one of greatest complexity or, as I have often put it, "the auto-immune disorder par excellence."

4. *Some Speculations as to the Pathogenesis of S.L.E.:* As stated above, both heteroimmunization and iso-immunization can be reproduced experimentally. Furthermore, iso-immunization occurs in the clinic in the form of acute hemolytic disease of the newborn and is seen in the transfusion reactions of incompatibility. Many attempts have been made to induce *auto*-immunization experimentally, but by and large they have been unsuccessful. For this reason, and stemming from the time of Ehrlich's dictum of "horror autotoxicus," some observers have rejected the possibility of auto-immunization, and have concluded that the various clinical disorders for which this concept is presumed are *apparently* of immunologic nature

but not *actually* so. We have contended that since—for example, in auto-immune hemolytic anemia—a substance is present in the serum which reacts specifically against red cells, that it is a gamma globulin, that it becomes adherent to the red cell surface and gives a positive Coombs' test, that it can be eluted from the red cell surface, that the red cell shows spherocytosis and that a heteroantibody injected in vivo may induce similar changes of anemia and spherocytosis, and that ACTH and the corticosteroids reduce the *concentration of "antibody" globulin*—for all these reasons, we have contended that this is an *immuno*hemolytic anemia. If this is correct, how, then, does an antibody against the patient's red cells develop? This presupposes the prior development of an auto-antigen. One may postulate either that this occurs following alteration of the red cell surface which, being altered, is no longer "recognized" by the antibody producing cells and is thus potentially antigenic, or that a "hapten" mechanism is involved. In the latter process a drug or chemical may attach itself to the surface of the cell (cf. above, as with quinidine and platelets), thus altering the cell and rendering it capable of becoming antigenic.

This relatively simple explanation should be susceptible of experimental proof, but unfortunately this has not as yet been obtainable except in the case of thyroiditis (Hashimoto type).[39] In systemic lupus, with its great variety of possible auto-immune disorders occurring either simultaneously or sequentially, one all-embracing explanation is even more difficult. Only one well defined cause for a systemic "lupus-like" disorder has been demonstrated, i.e., the drug Apresoline. Here, the continued use of a relatively simple chemical may result in a syndrome indistinguishable from that of S.L.E.[40] It is possible that the chemical acts as a hapten which, in association with various blood and blood vessel constituents of S.L.E., becomes antigenic. Many other as yet *unknown* agents may have a similar effect. In this regard one may mention penicillin [41] which, when it has resulted in reactions, has at times been associated with lupus-like lesions and a positive L.E. test.

Another possible factor in pathogenesis may have to do with the sex of the patient with lupus. By all available statistics the disorder occurs almost entirely in women, particularly in young women of childbearing age. All the cases reported above occurred in women, and the only cases of S.L.E. in males we have seen had a history of prolonged drug administration—in two, Apresoline; in the third, penicillin. The matter of possible endocrine abnormalities has been discussed in several publications [42] but is not convincing. We have conceived of the possibility that the uterus, more particularly the menstruating endometrium, may be a factor in the development and progression of S.L.E. in some women. One may speculate that the active endometrium in the childbearing age affords an ideal physical milieu for the production of auto-antigens from altered blood cells and blood vessels. In its resting phase the endometrium is thin, measuring only a few millimeters,

but with ovulation it becomes greatly thickened, showing at first marked infiltration with polymorphonuclear cells, then with platelets. Large pools of stagnant blood appear. As the endometrium expands further, "spiral" arteries develop, and when the superficial layers of the endometrium slough off, these arteries break and hemorrhage occurs. It is possible that these altered constituents of blood and blood vessels, either directly or through the mediation of unknown haptens, may act as auto-antigens, with the resultant development of auto-antibodies in some cases. This would probably be accelerated in individuals who (a) are potent antibody producers, and (b) have some other "trigger" mechanism, such as unusual exposure to drugs or chemicals. This process could conceivably be accentuated and facilitated by the periodic character of the catamenia, corresponding to frequent "booster" injections in an immunization procedure.

Summary

1. The hematologic abnormalities of systemic lupus include a positive Coombs' test, with or without hemolytic anemia; thrombocytopenic purpura; leukopenia, at times severe; a positive serologic test for syphilis; a hemorrhagic disorder due to circulating anticoagulants, and the L.E. factor. They may be said to be just as representative of the disease as are the "onion-skin" vascular lesions in the spleen, the "wire-loop" lesions in the kidneys, or the vascular and "collagen" lesions elsewhere. The various hematologic abnormalities, including the L.E. factor, may be considered as "auto-immune" in nature with the development of auto-antibodies against various antigens in the blood cells or plasma. The L.E. factor is probably an abnormal auto-antibody directed against a constituent of the leukocyte nucleus. Other leukocytic antibodies may also occur in the disease.

2. If the various hematologic lesions of systemic lupus are considered to be "auto-immune," it is likewise possible that the vascular lesions (vasculitis), with resultant skin lesions (lupus), arthritis, nephritis, pleuritis, endocarditis, etc., may also be due to auto-antibodies, but in this instance directed against small blood vessels. Indeed, the entire disease of systemic lupus may be a complex of immunologic disturbances affecting (1) blood cells and other blood constituents, and (2) small blood vessels. The L.E. factor may be considered as only *one* of the immunologic abnormalities of lupus; thus, its lack in a given case does not necessarily rule out the presence of the disease.

3. "Idiopathic" thrombocytopenic purpura (ITP) is often a prodrome of systemic lupus—thus, every case of ITP in a young woman should be suspected of being lupus. "ITP" need not be considered to be symptomatic of lupus, but simply as one part of the generalized disease. Combinations of ITP with auto-immune hemolytic anemia are even more likely to be examples of lupus, whether or not other manifestations of systemic lupus are

present. Dissemination of the lupus process may be accelerated by splenectomy.

4. The presence of complex mixtures of auto-antibodies in systemic lupus suggests that numerous antigens (perhaps altered blood cells, altered blood plasma constituents, altered small blood vessels) are concerned. Since the great majority of cases of the disease occur in women, the possibility is present that antigen development may take place in the menstruating endometrium. Here, at monthly intervals, alterations in blood cells, blood plasma constituents and small blood vessels (spiral arteries) take place. One may speculate that in certain women these altered cells, plasma factors and blood vessel constituents become auto-antigenic, thus leading to the formation of several types of auto-antibodies against both blood constituents and small blood vessels, and thus to the complex disease known as systemic lupus. The periodic character of the menstrual cycle might well aid in auto-antibody formation. Such a speculation does not preclude the possibility of auto-immunization by other mechanisms, as in the relatively uncommon cases in males.

Summario in Interlingua

1. Le anormalitates hematologic de systemic lupus erythematose include positivitate del test de Coombs (con o sin anemia hemolytic), purpura thrombocytopenic, leucopenia (a vices de grado sever), positivitate del test serologic pro syphilis, un disordine hemorrhagic in consequentia del circulation de anticoagulantes, e le presentia del factor de lupus erythematose (L.E.). Iste anormalitates hematologic es probabilemente tanto representatori pro le morbo como le anormalitate splenic de lesiones vascular a "pelle de cibolla," le anormalitate renal del lesiones a "ansas de filo metallic," o le anormalitates que occurre alterubi in le forma de lesiones vascular e "collagenic." Le varie anormalitates hematologic, incluse le presentia del factor de L.E., pote esser considerate como de natura "auto-immun," con le disveloppamento de auto-anticorpore contra varie antigenos in le cellulas o le plasma del sanguine. Le factor de L.E. es probabilemente un auto-anticorpore anormal dirigite contra un constituente del nucleo leucocytic. Il es possibile que ancora altere anticorpores leucocytic occurre in le morbo.

2. Si le varie lesiones hematologic de systemic lupus erythematose pote esser considerate como de natura "auto-immun," il es etiam possibile que le lesiones vascular (vasculitis)—con le resultante lesiones cutanee (lupus), arthritis, nephritis, pleuritis, endocarditis, etc.—representa equalmente le effectos de auto-anticorpores, ben que in iste caso de auto-anticorpores dirigite contra micre vasculos de sanguine. De facto, le integre morbo de systemic lupus erythematose es possibilemente un complexo de disturbationes immunologic que affice (1) cellulas e altere constituentes del sanguine e (2) micre vasos de sanguine. Le factor de L.E. pote esser considerate como solmente *un* del anormalitates immunologic in lupus erythematose, de maniera que su absentia in un caso particular non exclude necessarimente le presentia del morbo.

3. "Idiopathic" purpura thrombocytopenic (IPT) es frequentemente un prodrome de systemic lupus erythematose. Assi, omne occurrentia de IPT in un juvene femina debe inspirar le suspicion que lupus pote esser presente. Il non es necessari considerar IPT como symptomatic de lupus sed simplemente como un del partes del morbo generalisate. Le combination de IPT con auto-immun anemia hemolytic es mesmo plus suspecte. Illo indica quasi certemente le presentia de lupus, si o non altere

manifestationes de lupus es manifeste. Le dissemination del processo de lupus pote esser accelerate per splenectomia.

4. Le presentia de complexe mixturas de auto-anticorpores in systemic lupus erythematose suggere le production de numerose antigenos—como forsan alterate cellulas sanguinee, alterate constituentes del plasma del sanguine, o alterate micre vasos. Proque le grande majoritate del casos de iste morbo occurre in feminas, il existe le possibilitate que le disveloppamento de antigenos occurre in le endometrio menstruante. Hic il occurre, a intervallos mensual, alterationes del cellulas sanguinee, del constituentes del plasma del sanguine, e del micre vasos de sanguine (arterias spiral). Il pare permissibile specular que in certe feminas iste alterate cellulas, factores de plasma, e constituentes vascular deveni antigenic, effectuante assi le formation de plure typos de auto-anticorpore contra elementos sanguinee e micro-vascular e consequentemente le disveloppamento del morbo complexe que es cognoscite como systemic lupus erythematose.

BIBLIOGRAPHY

1. Baehr, G., Klemperer, P., and Schifrin, A.: Diffuse disease of peripheral circulation (usually associated with lupus erythematosus and endocarditis), Am. J. Med. **13**: 591–596, 1952.
2. Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosus, Arch. Path. **32**: 569, 1941.
3. Klemperer, P.: The concept of collagen diseases, Am. J. Path. **26**: 505, 1950.
4. Kaiser, I. H.: The specificity of periarterial fibrosis of the spleen in disseminated L.E., Bull. Johns Hopkins Hosp. **71**: 31, 1942.
5. Hargraves, M. M., Richmond, H., and Morton, R.: Presentation of two bone marrow elements: the "tart" cell and "L.E." cell, Proc. Staff Meet., Mayo Clin. **23**: 25–28, 1948.
6. Hargraves, M. M.: Production in vitro of the L.E. cell phenomenon; use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus, Proc. Staff Meet., Mayo Clin. **24**: 234, 1949.
7. Dameshek, W., and Reeves, W. H.: Exacerbation of lupus erythematosus following splenectomy in "idiopathic" thrombocytopenic purpura and auto-immune hemolytic anemia, Am. J. Med. **21**: 4 (Oct.) 1956.
8. Dubois, E. L., and Martel, S.: Discoid lupus erythematosus: an analysis of its systemic manifestations, Ann. Int. Med. **44**: 482, 1956.
9. Kaposi, M. K.: Neue Beiträge zur Kenntnis des Lupus erythematosus, Arch. f. Dermat. u. Syph. **4**: 36, 1872.
10. Osler, W.: On the visceral complications of erythema exudativum multiforme, Am. J. M. Sc. **110**: 629, 1895.
11. Jadassohn, J.: Handbuch der Hautkrankheiten, 1904, Vol. 3, F. Mraeck, Berlin, p. 298.
12. Libman, E., and Sacks, B.: A hitherto undescribed form of valvular and mural endocarditis, Arch. Int. Med. **33**: 701, 1924.
13. Michael, S. R., Lufti Vural, I., Bassen, F. A., and Schaefer, L.: The hematologic aspects of disseminated (systemic) L.E., Blood **6**: 1059, 1951.
14. Dubois, E. L.: Acquired hemolytic anemia as the presenting syndrome of lupus erythematosus disseminatus, Am. J. Med. **12**: 197, 1952.
15. Dameshek, W.: "Auto-immune" hematologic disorders, International Society of Hematology, V (Paris) Congress, 1954.
16. Haserick, J. R., and Long, R.: Systemic lupus erythematosus preceded by false-positive serologic test for syphilis: presentation of five cases, Ann. Int. Med. **37**: 559, 1952.
17. (a) Lee, S. L., and Sanders, M.: A disorder of blood coagulation in systemic lupus erythematosus, J. Clin. Investigation **34**: 1814, 1955.

(b) Conley, C. L.: Disorders of the blood in disseminated lupus erythematosus, Am. J. Med. **13**: 1, 1952.

(c) Stefanini, M., and Dameshek, W.: Hemorrhagic disorders, 1955, Grune & Stratton, New York.

18. Lee, S. L., Michael, S. R., and Vural, I. L.: The L.E. (lupus erythematosus) cell. Clinical and chemical studies, Am. J. Med. **10**: 446, 1951.

19. (a) Dameshek, W.: Acquired hemolytic anemia. Physiopathology with particular reference to auto-immunization and therapy, Proceedings of the III International Congress of the International Society of Hematology, 1951, Grune & Stratton, New York, p. 120.

(b) Dameshek, W.: Hemolytic anemia. Direct and indirect indications, pathogenetic mechanisms and classifications, Am. J. Med. **18**: 315, 1955.

(c) Young, L. E., and Miller, G.: Differentiation between congenital and acquired forms of hemolytic anemia. Observations in 47 cases of hereditary spherocytosis and 24 cases of auto-immune hemolytic disease, Am. J. M. Sc. **226**: 664, 1953.

(d) Dausset, J., and Malinvaud, G.: Les anémies hémolytiques acquises avec auto-anticorps. Evolution, pronostic et traitement d'après l'étude de 54 cas, Semaine d. hôp. Paris **30**: 3130, 1954.

20. Evans, R. S., Takahashi, K., Duane, R., Payne, R., and Liu, C.: Primary thrombocytopenic purpura and acquired hemolytic anemia. Evidence for a common etiology, Arch. Int. Med. **87**: 48, 1951.

21. Stefanini, M., Chatterjea, J. B., Dameshek, W., Zannos, L., and Santiago, E. P.: Studies on platelets. II. The effect of transfusion of platelet-rich polycythemic blood on the platelets and hemostatic function in "idiopathic" and "secondary" thrombocytopenic purpura, Blood **7**: 53, 1952.

22. Harrington, W. J., Minnich, V., Hollingsworth, J., and Moore, C. V.: Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura, J. Lab. and Clin. Med. **31**: 1, 1951.

23. Tullis, J. L.: Platelet antibody tests in the diagnosis of purpura, New England J. Med. **249**: 591, 1953.

24. Dausset, J., and Malinvaud, G.: Examen critique des methodes immunologiques employées pour l'étude des purpuras thrombopéniques, Sang **28**: 1, 1957.

25. Ackroyd, J. F.: The pathogenesis of thrombocytopenic purpura due to hypersensitivity to Sedormid, Clin. Sc. **7**: 249, 1949.

26. (a) Weisfuse, L., Spear, P. W., and Sass, M.: Quinidine induced thrombocytopenic purpura, Am. J. Med. **17**: 414, 1954.

(b) Bolton, F. G., and Dameshek, W.: Thrombocytopenic purpura due to quinidine. I. Clinical studies, Blood **11**: 527, 1956. II. Serologic mechanisms, Blood **11**: 547, 1956.

27. Rabinovitz, Y., and Dameshek, W.: Systemic lupus erythematosus (S.L.E.) occurring after "idiopathic" thrombocytopenic purpura, in preparation.

28. (a) Goudsmit, R., and van Loghem, J. J., Jr.: Studies on the occurrence of leucocyte-antibodies, Vox Sanguinis **3**: 58–66, 1953.

(b) Dausset, J., Nenna, A., and Brecy, H.: Leukoagglutinins. V. Leukoagglutinins in chronic idiopathic or symptomatic pancytopenia and in paroxysmal nocturnal hemoglobinuria, Blood **9**: 696, 1954.

29. Miescher, P., and Holländer, L.: Les hémopathies par 'auto-anticorps,' Rev. méd. de la Suisse Rom. **75**: 398, 1955.

30. Seligmann, M., and Hanau, C.: Leuco-précipitine. II. Mise en évidence d'une réaction de précipitation entre des extraits leucocytaires et le sérum de malades atteints de lupus érythémateux disséminé, Vox Sanguinis **2**: 270–282, 1957.

31. Moore, J. E., and Lutz, W. B.: The natural history of systemic L.E. An approach to its study through chronic biologic false-positive reactors, J. Chron. Dis. **1**: 297, 1955.

32. Clark, W. G., and Jacobs, E.: Experimental non-thrombocytopenic vascular purpura. A review of the Japanese literature with preliminary confirmatory report, Blood **5**: 320, 1950.

33. (a) Dameshek, W.: Acute vascular purpura: "an immuno-vascular disorder," Blood **8**: 382, 1953.

(b) Kreidberg, M. B., Dameshek, W., and Latorraca, R.: Acute vascular (Schönlein-Henoch) purpura—an immunologic disease? New England J. Med. **263**: 1014–1018, 1955.

(c) Adelson, E., Heitzman, E. J., and Fennessey, J. F.: Thrombohemolytic thrombocytopenic purpuras, Arch. Int. Med. **94**: 42, 1954.

34. Bernard, J., Mathé, G., and Israel, L.: Clinical studies on the immunologic aspect of the physiopathology of the Schönlein-Henoch syndrome, International Society of Hematology VI (Boston) Congress, 1956.

35. McCombs, R. P., Patterson, J., and McMahon, E.: Syndrome associated with "allergic vasculitis," New England J. Med. **255**: 251–261, 1956.

36. Rich, A. R., and Gregory, J. E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp. **72**: 65, 1943.

37. Schuman, R. L.: The hemagglutination test for rheumatoid arthritis. I. An immunological analysis of the factors involved in the reaction, J. Immunol. **69**: 27, 1952.

38. Cavelti, P. A., and Cavelti, E. S.: Studies on the pathogenesis of glomerulonephritis: production of glomerulonephritis in rats by means of autoantibodies to kidney, Arch. Path. **40**: 158, 1945.

39. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, R. W.: Chronic thyroiditis and autoimmunization, J. A. M. A. **164**: 1439, 1957.

40. Shackman, N. H., Swillr, A. I., and Morrision, M.: A syndrome simulating acute disseminated L.E. Appearance after hydrolazine (Apresoline) therapy, J. A. M. A. **155**: 1492, 1954.

41. Walsh, J. R., and Zimmerman, H. J.: Demonstration of the L.E. phenomenon in patients with penicillin hypersensitivity, Blood **8**: 65, 1953.

42. Harvey, A. McG., Schulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic lupus erythematosus; review of the literature and clinical analysis of 138 cases, Medicine **33**: 291, 1954.

43. (a) Miescher, P.: Nucleophagocytose et phénomène L.E., Schweiz. med. Wchnschr. **83**: 1042, 1953.

(b) Miescher, P., Fauconnet, M., and Béraud, T.: Immuno-nucléo-phagocytose expérimentale et phénomène L.E., Exper. Med. and Surg. **11**: 173, 1953.

(c) Miescher, P.: The antigenic constituents of the neutrophilic leukocyte with special reference to the L.E. phenomenon, Vox Sanguinis **2**: 145, 1957.

44. Mellors, R. C., Ortega, L. G., and Holman, H. R.: Role of gamma globulin in pathogenesis of renal lesions in systemic lupus erythematosus and chronic membranous glomerulonephritis, with an observation on the lupus erythematosus cell reaction, J. Exper. Med. **106**: 191, 1957.

CANCER OF THE HEAD AND NECK *

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SINCE the internist may be the first physician to see a patient, he should be thoroughly familiar with the problems of head and neck cancer. This paper has been written with the idea of reviewing a number of the important factors in the early diagnosis and treatment of cancer of the head and neck.

CANCER OF THE MOUTH

The term "mouth cancer" is commonly used to define those malignant tumors which arise in the mucous membrane of the oral cavity, beginning anteriorly at the mucocutaneous junction of the lips and extending posteriorly to the level of the free edge of the soft palate, the tonsil and the base of the tongue.[1]

Incidence and Etiology: Oral cancer accounts for more than 5% of all human cancers. It is a disease mainly of middle and old age, but it may occur in the young and even in infants. By far the great majority of carcinomas of the mouth are found in men. Although the actual cause or causes of oral cancer are not known, considerable knowledge has been accumulated concerning many factors which seem to be important in pathogenesis.

Long-standing exposure to sunshine, wind and frost (farmers, sailors, etc.) is by far the most frequent predisposing factor in carcinoma of the lower lip.[2] Chronic exposure to sunshine over a period of years results in dryness and hyperkeratosis of the lower lip. This hyperkeratosis may gradually develop into a superficial area of ulceration which later becomes indurated and is found to be carcinomatous. Blond-skinned individuals are more easily affected by the sun, and carcinoma of the lower lip is very rare in Negroes.

In the past, about 20% of all male patients with cancer of the tongue had chronic syphilis, as contrasted with about 4% of syphilis in males of a similar age group without cancer of the tongue.[1] The actual causal relation between oral cancer and syphilis is not known. Some authorities have implicated therapy, such as with arsenic, as an important factor. In more recent surveys, the incidence of positive serologic tests for syphilis has been lower. This may be accounted for by the newer forms of therapy for syphilis.

Mills [3] has found a higher incidence of smokers among patients with buccal mucosa cancer and respiratory tract cancer than in the general popula-

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tion. Carcinoma of the buccal mucosa is more common in individuals who habitually chew tobacco. The high incidence of intra-oral cancer in India has been attributed to the chewing of betel nut, together with a cheap form of tobacco.[4] Ackerman and del Regato [2] dispute the importance of pipe-smoking in the etiology of carcinoma of the lip. They point out the infrequent occurrence of carcinoma of the upper lip, which is equally affected by the heat of the pipe-stem; the not infrequent occurrence of carcinoma of the lower lip toward the midline and its rather infrequent occurrence at the buccal commissure, where most pipe-smokers hold the stem; and the low incidence of pipe-smokers among patients with carcinoma of the lower lip.

Poor oral hygiene, malnutrition, trauma and other forms of localized irritation are other important factors. Hypertrophy of the mucous membrane due to repeated trauma, such as biting or malfitting dentures, must be differentiated from true tumors. This is a danger signal indicating chronic irritation which, if it continues, might cause malignancy. Ahlbom has called attention to the high incidence of carcinoma of the oral cavity, the pharynx and the esophagus in Swedish women, and its possible relation to the also high incidence of sideropenia (Plummer-Vinson syndrome).[5] This disease is due to malnutrition, and is considered by some to be a true precancerous condition.

Premalignant Lesions: 1. Leukoplakia and hyperkeratosis. Hyperkeratosis and especially leukoplakia are important premalignant lesions. Leukoplakia is a hypertrophy of the squamous epithelium which, under the microscope, has the appearance of the hyperkeratosis seen in the skin. The actual difference is that, in the mouth, where the surface of the mucous membrane is constantly moistened, the lesion does not peel off as does hyperkeratosis on the skin. Ward and Hendrick [6] have classified leukoplakia into three groups. The first group is the so-called acute group of leukoplakia, which is thickened and sometimes actually ulcerated or even papillomatous. This group is more apt to become malignant than is the second group. The second group is that of chronic leukoplakia, which sometimes lasts as long as 20 years. This form is usually more diffuse, and appears as a thin white film over the surface of the tongue, buccal mucous membrane or the palate. The third group is an intermediate group (subacute type). They believe that this group probably represents the early form of a more chronic variety, and stands intermediary between types one and two, usually behaving like the latter. If the leukoplakia is fixed or ulcerated or papillomatous, or contains a hard nodule, biopsy should be made to rule out cancer. This biopsy should be taken at the margin in an area where tumor is suspected.

The treatment of leukoplakia should begin by removing any form of irritation, such as ill-fitting dentures, bad teeth, excessive smoking, and hot and spicy foods. If the removal of the irritating factors does not cause the leukoplakia to disappear, and if definite proof of cancer is lacking, the areas may be treated in one of several ways, including electrodesiccation, cautery

or surgery. Estrogens have been successful in some cases of leukoplakia in postmenopausal women.

2. Epithelial papilloma. These lesions are a proliferation of squamous epithelium developing into folds and, later, finger-like projections. It is important to differentiate them from inflammatory papilloma or papillitis. Since they tend to become malignant, they should be removed surgically.

Pathology: Carcinoma of the oral cavity may be exophytic, infiltrating or ulcerating. The most frequent histologic type of cancer of the mouth is epidermoid carcinoma (about 90%). Adenocarcinoma is occasionally found and is most often seen on the palate. It has its origin from minor salivary glands. About 75% of oral cancers are well differentiated, and the more malignant varieties, such as anaplastic carcinomas and lympho-epitheliomas, have an affinity for structures in the posterior oral cavity, particularly in the tonsillar region and base of the tongue. Lymphosarcomas are also found in the posterior oral cavity.

Diagnosis: Since all cancers of the oral cavity are either visible or palpable, systematic inspection and palpation are the most important procedures in diagnosis. All that is needed is a good light, head mirror, tongue spatulas, finger-cots and a laryngeal mirror.

The lips should be inspected first, and particular attention should be paid to the vermilion borders. Then with the aid of two tongue blades, used to maneuver the tongue within the oral cavity, all areas should be viewed in order. During the examination of the intra-oral cavity it is a common mistake to have the patient stick out his tongue. To examine the floor of the mouth, the tip of the tongue should be raised to the roof of the mouth. With a finger-cot on the index finger, bimanual palpation should be done, and palpation of the base of the tongue should not be omitted. The only region of the oral cavity not accessible to direct vision is the base of the tongue, and this can be examined well by means of palpation as well as visualization by means of the laryngeal mirror. Any suspicious lesion of the mouth should be considered cancer until a biopsy rules this out. Repeated biopsies may be necessary, since the first biopsy may be from an area showing only chronic inflammation. It is also important to establish whether the lesion present has been chronic and/or progressive.

Cancer of the Lip: In the United States, cancer of the lower lip is the most common form of oral cancer.[2] The common site of cancer of the lower lip is on the portion of the vermilion border which lies outside of the line of contact with the upper lip at a point equally distant from midline and buccal commissure. It also occurs in the middle one third of the lower lip and, less frequently, at the buccal commissure. The majority of lesions are exophytic, but may be ulcerating or verrucous. Metastases occur later, and less frequently, than from other forms of oral cancer. The submaxillary nodes are most frequently involved, and other cervical node metastases are rare without submaxillary metastases. Involvement of the opposite side

is rare unless the lesion is near or beyond the midline. When the lesions have ulcerated the skin, contralateral lesions are more common. The verrucous lesions tend to remain localized.

The most important clinical finding is that of a blister. Recurrent scabs are also common. Leukoplakia should arouse suspicion. Growth is characteristically slow and asymptomatic until in an advanced stage. If the clinical impression is malignant disease, repeated biopsies should be taken (sufficiently deep) from the borders of the lesion, if the initial biopsy does not confirm the impression.

Cancer of the upper lip is relatively uncommon. It occurs usually near the midline. It is usually exophytic and superficially ulcerating, though it may be extensively infiltrating or verrucous. Metastases are frequent and early. The tumors grow more rapidly than does cancer of the lower lip.

Cancer of the Tongue: This is the second most common form of intraoral cancer. Malignant tumors of the tongue cause more deaths each year than does any other head and neck cancer, including thyroid neoplasms. Cancer of the base of the tongue is one quarter to one sixth as common as cancer of the mobile portion of the tongue (anterior two thirds).

Cancers of the mobile portion of the tongue occur most frequently on the lateral border, and are predominantly infiltrating, although they may be exophytic or ulcerating. Leukoplakia often shades imperceptibly into carcinoma of the tongue, and microscopic examination is important. When carcinoma arises from leukoplakia, it is often multicentric in origin. About 70% of carcinomas of the mobile portion of the tongue metastasize to cervical nodes, and in advanced disease distant metastases are not uncommon.

Most of the malignant tumors of the base of the tongue are carcinomas, lympho-epitheliomas and lymphosarcomas. Epidermoid carcinoma of the base of the tongue is one of the most infiltrating types of cancer of the upper air passages. Fissure-like ulcerations may be found. The carcinoma frequently extends on both sides of the midline. The majority are well differentiated epidermoid carcinomas, but anaplastic carcinomas are not unusual in this area.

Most carcinomas of the tongue are symptomatic, and yet there is usually a delay of several months before definitive diagnosis is made. Tumors arising from the anterior two thirds present with the following symptoms: awareness of an oral mass, local tenderness or burning pain. These symptoms also occur in tumors arising at the base of the tongue, but, in addition, there is frequently otalgia, dysphagia or dysphoria. Secondary infection is common. In cancer of the tongue, cervical node metastases may be the earliest finding.

Lympho-epitheliomas are usually nonulcerating, polypoid, unilateral tumors. Voluminous upper cervical nodes are commonly present, and there is frequently generalized disease. Lymphosarcomas are usually nonulcerated, extensive and bilateral. Regional nodes are almost always found, and

bilateral discrete nodes are common. Lympho-epitheliomas and lymphosarcomas may develop silently and may be discovered only on examination or by the presence of cervical adenopathy.

Cancer of the Tonsil: Cancer of the tonsil is fairly common. Epidermoid carcinomas, lympho-epitheliomas and lymphosarcomas are the common tumors found in the tonsillar region. The epidermoid carcinomas are usually exophytic, superficially ulcerated tumors which spread superficially. The majority are undifferentiated. Regional node metastases are fairly common. The important early symptoms are slight pharyngeal discomfort, sensation of foreign body with slight odynophagia, and enlarged cervical nodes. Pain, otalgia and dysphagia occur later.

Lympho-epitheliomas are usually smooth, mostly submucous, somewhat lobulated tumors which spread superficially. Lymphosarcomas develop submucously and may become very large without presenting an ulceration. As in lympho-epithelioma and lymphosarcoma of the base of the tongue, cervical node involvement is predominant. Lympho-epitheliomas, as well as lymphosarcomas, are frequently asymptomatic, and rapidly growing adenopathy is often the first finding. Lymphosarcomas may also present as obstructive, inflammatory or systemic symptoms. The inflammatory symptoms are recurrent pharyngitis and fever.

Cancer of the Buccal Mucosa: In the United States, cancer of the buccal mucosa is one third to one quarter as common as cancer of the tongue. In certain areas of the United States where chewing tobacco is a common habit, cancer of the buccal mucosa is almost as common as cancer of the tongue. The tumors are usually exophytic, but may be ulcerating and verrucous. The onset of the disease may be insidious. Some of the more common symptoms include trismus, submaxillary adenopathy, bleeding and pain. Multicentric origin of buccal cancer is common. The prognosis for the exophytic tumor depends upon the stage, and in general the prognosis for ulcerated tumors is poor and for verrucous tumors is good.

Cancer of the Floor of the Mouth: Cancer of the floor of the mouth is fairly common. The lesions appear as fissure-like ulcerations or superficial ulcerations. Regional node metastases are common and often bilateral. The patient may be aware of an indurated growth. Later he may notice otalgia, hypersalivation and difficulty in speech. Bleeding is sometimes noted.

Cancer of the Gingiva: Cancer of the lower gingiva accounts for about 5% of oral cancers. They may be exophytic, ulcerating or verrucous. Cervical metastases are common. The diagnosis should be suspected when there are ill-fitting dentures, a suspect alveolar abscess, bleeding of the gum, otalgia or trismus. An x-ray of the mandible should be taken in all cases. Cancer of the upper gingiva is uncommon.

Cancer of the Palate: Cancer of the palate is uncommon in this country. Minor salivary gland tumors are more common in the upper palate than are

epidermoid carcinomas. In India, epidermoid carcinomas of the hard palate are common, and the increased frequency has been attributed to the smoking of the cheap cigar, chutta. The smokers of chutta often resort to reverse smoking, putting the lighted end of the cigar in the mouth. Well differentiated epidermoid carcinomas are more common in the soft palate than in the hard palate.

Treatment of Oral Cancer

The most important point in determining the prognosis of oral cancer is early diagnosis (table 1).

In general, there is agreement that the treatment of choice for lesions arising in the posterior part of the oral cavity, such as the tonsil and base of the tongue, is irradiation. Lesions of the posterior third of the base of the tongue, which are well lateralized and small, can be removed surgically. Lesions involving the dorsum and the middle of the tongue are also usually

Table 1*

Five-Year Cure Rates in Mouth Cancer†

Site of Primary Lesion of Cancer	Percentage Five-Year Cure Rates in All Cases (All Cancers, Both Early and Advanced)	Percentage Five-Year Cure Rate in Early Cases (Primary Lesion Less Than 2 cm.)
Lip	70	86
Tongue	30	55
Floor of mouth	20	50
Mucosa of cheek	24	60
Palate (hard and soft)	30	57
Gums	32	38
Tonsil	20	50

* From Head and Neck Service of Memorial Hospital.[1]
† Period of 1935–1942.

controlled by radiation therapy. It is interesting that Berridge and James recommended an elliptic excision for tumors involving the middle third of the tongue.[7] They obtain continuity of the tongue by closing the surgical defect with fine interrupted chromic catgut sutures.

Lympho-epitheliomas and lymphosarcomas are generally radiation problems.

On the other hand, there is considerable controversy concerning the treatment of choice for tumors arising on the more anterior aspects of the oral cavity. This controversy has been well illustrated in a series of papers in the *American Journal of Roentgenology, Radiation Therapy and Nuclear Medicine*.[8–11] To help resolve some of the confusion, some of the general principles regarding surgical and radiation indications will be outlined.

In an address to the American Roentgen Ray Society, Slaughter listed the following as indications for surgical treatment of oral cancers:[12]

A. Definite Indications:

1. Tumors recurring or persisting after radiation. The tissue radiation tolerance in such a situation has largely been exhausted.

2. Bone invasion, excluding minor erosion. A sterilizing dose delivered to this area will be sufficient to cause the bone to undergo radionecrosis.

3. Tumors of minor salivary glands. These are notoriously radioresistant and rarely radiocurable. Radiation may be tried when these tumors are inoperable.

4. Adamantinomas or ameloblastomas.

5. Sarcomas and neurogenic tumors (excluding lymphosarcomas, which are a radiation problem).

6. Radiation cancer.

7. Cervical lymph node metastases. When the disease is technically inoperable, radiation may be tried.

B. Preferable Indications:

1. Superficial, exophytic lesions, especially about the tip of the tongue.

2. Youth. The late effects of radiation, including radiation cancer, are the main dangers. (Radiation cancers in these areas are rare, but there is a danger of chronic exposure to predisposing causes in an irradiated area.)

3. Isolated keratinizing squamous cell lesions of the base of the tongue and the pharyngeal wall. They are not usually radiosensitive, and may manifest themselves initially with cervical lymph node metastases. They should be removed by neck dissection and incontinuity pharyngotomy.

C. Optimal Indications:

Small and superficial oral cancers, particularly those of the tip of the tongue and the lateral border. Surgery is recommended here because of the simplicity of the procedure and because it produces less discomfort to the patient.

Ackerman and del Regato [13] and Garland [14] have outlined the general principles of cancer radiation therapy. As has been pointed out, the establishment of a scale of radiosensitivity of malignant tumors is the result of clinical observation. In highly radiosensitive tumors, such as lymphosarcoma or lympho-epithelioma, radiation is the undisputed form of "curative" therapy. In the moderately radiosensitive tumors, such as basal cell carcinoma of the skin, and epidermoid carcinoma of the skin, mucous membrane and mucocutaneous junction, radiotherapy may be most effective, but the choice of therapy should take into consideration other concomitant circumstances besides favorable radiosensitivity. Poorly radiosensitive tumors or radioresistant tumors such as the soft tissue sarcomas and malignant melanomas are not "radiocurable," but when no other form of therapy can be offered to these patients, a trial with radiation is worth while.

"Radiocurability" depends mostly upon radiosensitivity. Other factors, however, influence the "radiocurability" of the tumor, and some of the most important ones include vascularity (increased radiosensitivity with increased vascularity), site of origin, accessibility, and degree of differentiation (the more undifferentiated, the more radiosensitive).

In the treatment of oral cancer, external roentgenotherapy and curietherapy are both popular. With skilled radiotherapy, serious side-effects usually can be avoided; but even with skilled therapy, reactions such as edema, inflammation and pain must be expected during the acute phase of therapy. In some forms of oral cancer, surgery produces functional disability. A good rule is that the nearer the tumor is toward the base of the tongue, the poorer the functional result with surgery. In some instances the five-year survival rate free of disease is better with surgery, and when this is true, surgery should not be denied, because most patients accommodate well to the mild or moderate functional disability.

The five-year survival rate free of disease for carcinoma of the lower lip should approximate 95% with either radiation or surgery. In spindle cell carcinomas of the upper lip, surgery is preferred. In some centers, choice of therapy may depend upon the skill of the therapist available. The V-shaped excision is a minor procedure used for small lesions. It can be done under local anesthesia and does not require hospitalization. Surgical treatment of lesions which require excision of more than one fourth of the entire length of the lower lip require some form of cheiloplasty rather than a V-excision.

As has already been stated, the treatment of choice for cervical node metastases is surgery. The question of prophylactic neck dissection has been raised in patients with oral cancer. In general, prophylactic neck dissection for carcinoma of the lower lip is not indicated, because of the high "cure rate" and the low incidence of metastases without neck dissection. Prophylactic neck dissection for carcinoma of the tongue is still an open question.

Cancer of the Nasopharynx

The incidence of cancers of the nasopharynx can only be estimated, since even today many cases pass undiagnosed. In cancer centers, tumors of the nasopharynx are variously reported as making up between 0.5 and 1.0% of all cases of cancer.[2] The Chinese have an unusual predisposition to the development of cancer of the nasopharynx, particularly lympho-epitheliomas and lymphosarcomas. This high incidence of tumors of the nasopharynx in Chinese has been attributed to their living habits. It also occurs in Chinese who are raised in America, and this may be accounted for by the fact that they tend to retain many of their living habits.

Grossly, tumors of the nasopharynx may be ulcerated, globular or exophytic. Lymphosarcomas make up from one third to one-half of all primary tumors of the nasopharynx. The remaining number are mostly lympho-epitheliomas and some undifferentiated epidermoid carcinomas. The differentiated squamous cell carcinoma is very exceptional in this area.

Despite the emphasis which this point has already received, the fact remains that we rarely see a malignancy of the nasopharynx before one or more

complications have arisen.[15] Presenting complaints are often nasal obstruction, epistaxis, deafness, tinnitus, or enlargement of the cervical glands. Pain involving the distribution of the fifth cranial nerve is a fairly characteristic symptom. Neurologic complications occur in 35 to 50% of nasopharyngeal malignancies, and may present diverse manifestations. In addition to the fifth nerve, the third, fourth and sixth nerves are most frequently affected, because of their location in the middle cranial fossa. Horner's syndrome is a fairly common complication. Symptoms referable to the anterior or posterior cranial fossa are less frequently observed.

Early diagnosis is dependent upon careful examination of the nasopharynx in patients who have persistent symptoms referable to the middle ear and nasal passages, and in patients with cervical enlargements. The examination should include digital examination and an indirect mirror view by posterior rhinoscopy.

External roentgenotherapy is the treatment of choice, but in certain instances very useful adjuncts to this therapy should include intranasal radiation with radiocobalt, or septectomy.[16] In most instances, surgery is contraindicated in the treatment of nasopharyngeal malignancy.

An early lesion without cervical metastases offers the possibility of permanent cure. Cervical metastases, invasion of bone or evidence of cranial nerve involvement materially alters the prognosis. Carcinomas of the nasopharynx are highly radiosensitive, and in most instances the primary growth will completely regress under treatment, only to have the patient succumb to distant metastases.

Cancer of the Larynx

Carcinoma of the larynx is most frequently found in men in their fourth, fifth and sixth decades. The true incidence of carcinoma of the larynx cannot be given accurately because of the marked confusion in classification,[17] but it probably accounts for about 3% of all forms of cancer.

The classification used in this paper is the one given by Friedberg and Wallner [18] (figure 1).

1. Cordal (occurs in true cords, with normal mobility).
2. Endolaryngeal (occurs in a true cord, ventricle, false cord, or early subglottic invasion).
3. Subglottic.
4. Extracordal or extrinsic (occurs in epiglottic, arytenoid, arytenoepiglottic fold or pyriform sinus).

This classification is essentially that of Walsh, with minimal modification. The term "cordal carcinoma" is used instead of "intrinsic carcinoma" to avoid more confusion about the term "intrinsic."

Smoking is an important factor in chronic nonspecific laryngitis, polypoid degeneration of the vocal cords and in keratosis (including leukoplakia).[19] Polypoid degeneration and keratosis are precancerous conditions. Statis-

tical evidence indicates that cigarette smoking also is a factor in the etiology of laryngeal cancer.

Ogura has written an excellent article on the pathology of cancer of the larynx.[20] A partial summary of his results reveals that, of 59 surgical specimens, 55 tumors (93%) were characterized by ulceration or fungation and deep infiltration. Three were exophytic papillary structures, and infiltration was minimal. Fifty-six tumors (95%) were of the squamous cell variety; three were adenocarcinomas. The location of the primary tumor was a determining factor as to the frequency of invasion of the prelaryngeal node, the preëpiglottic space and the thyroid cartilage. A high incidence of metastases was demonstrated in impalpable nodes in extrinsic, subglottic and endopharyngeal carcinomas (57%, 50% and 31%, respectively). Im-

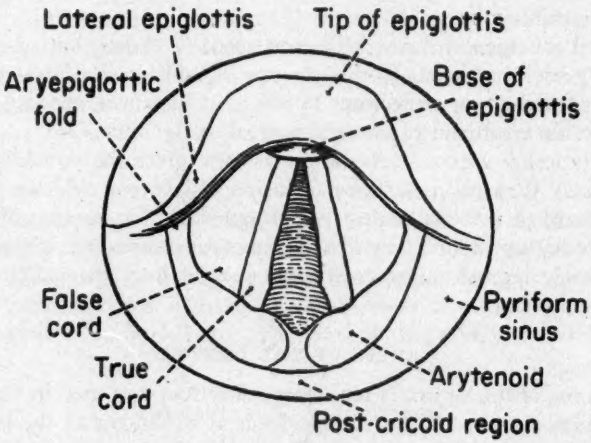

FIG. 1. The larynx as viewed through a laryngeal mirror.

palpable metastases observed in the deep cervical nodes were nearly always homolateral and rarely contralateral to the primary lesions. Therefore, initial accurate clinical classification of the primary lesion is important to determine the therapy that may have to be undertaken. In cancer of the larynx the demonstration of tumor invasion in the prelaryngeal nodes, thyroid cartilage or the preëpiglottic space is an important part of the prognostic findings, since there was a fair correlation between the invasion of these areas and the involvement of the deep cervical glands.

Kuhn et al., reporting on a large series of patients with cervical metastases, concluded that the site of the tumor, histologic grade of the tumor, and microscopic infiltrative nature of the tumor each significantly affected the likelihood of the occurrence of cervical metastases with patients with squamous cell carcinoma of the larynx.[21] Metastases occurred rarely in tumors confined to the cordal area, but occurred with increasing frequency

the further the tumors were located from this area. No metastases occurred from tumors Grade 1, but metastases occurred from tumors Grade 2 or more, with rapidly increasing frequency as the grade advanced. Predictions about cervical metastases based on palpation of the neck at time of diagnosis were frequently inaccurate.

One of the most important reasons for the poor prognosis of certain forms of cancer of the larynx is the delay between onset of symptoms and actual diagnosis. Friedberg and Wallner found that the average duration of symptoms between onset and diagnosis was seven months for cordal carcinoma, 8.7 months for endolaryngeal carcinomas, 13.4 months for subglottic carcinomas, and eight months for extracordal carcinomas.[18] These average figures did not include cases where symptoms had been present for several years. The delay in diagnosis is not solely due to the patient's delay in seeing a physician. Although practically every student knows that hoarseness persisting more than several weeks is a danger signal warning against cancer or tuberculosis, it is quite surprising that many practicing physicians are complacent about these symptoms. The widespread misuse of antibiotics has given many a physician a false sense of security. The responsibility for delays in diagnosis must be accepted in part by the internist, who is frequently the first one to see the patient. Hoarseness was present in every case of cordal and endolaryngeal carcinoma in Friedberg and Wallner's series. In addition, approximately one third of the patients with endolaryngeal carcinomas have throat discomfort. Although subglottic carcinomas usually do not produce symptoms until the lesion has invaded the vocal cord, or has caused some narrowing of the airway, it is of particular interest that the average duration of symptoms before diagnosis was 13.4 months. The symptoms usually seen with these types of carcinomas are hoarseness, or evidence of obstructive dyspnea. The most common symptom in the extracordal carcinoma was some form of throat discomfort (dysphagia, localized pain, or sensation of a foreign body). Hoarseness was the next most frequent symptom. The importance of chronic and heavy smoking in the etiology of cancer of the larynx has already been discussed, and should definitely raise the index of suspicion. Laryngeal and nasopharyngeal examinations are vital.

The prognosis of cordal carcinoma is excellent, and should approach 100% five-year cure rate. Similar results are obtained with radiation or surgery. When the disease is limited to a small area on the middle of the vocal cord, with complete preservation of the mobility of the cord, a simple surgical procedure, such as laryngeal fissure, thyrotomy or cordotomy, can be done readily. There is practically no operative risk, and healing occurs in eight to 10 days, with excellent results. When the cancer involves the entire cord from end to end, the mobility is still preserved, and the cancer is limited to the vocal cord, one again has the choice between surgery and radiotherapy. The surgery in such cases is more extensive than that

previously described. The functional result is usually not so good as that obtained with radiation. As a rule, the greater the fixation of the vocal cord, the more definite is the indication for surgery, because of the high incidence of cervical metastases. Other endolaryngeal cancers are usually most benefited by surgery. Subglottic cancer is essentially a surgical problem. When the disease is inoperable, radiation therapy should be tried. Until recently the prognosis for extrinsic carcinoma has been poor, and radiation has usually been the therapy of choice. Unpublished data from the Memorial Hospital have given more encouragement to extensive surgical procedures for carcinoma of the pyriform sinus. Leroux has obtained surprisingly good results with surgery and postoperative radiation.[22] Other workers have questioned the need for postoperative radiation if the surgery is complete.

There has been a recent swing to prophylactic neck dissections, together with total laryngectomy, because of the higher "cure rates" obtained, the high incidence of unsuspected, clinically impalpable nodes, and the fact that cervical metastases are usually unilateral. This procedure is recommended even in the absence of palpable cervical nodes because of the high incidence of metastatic nodes found at surgery which are unsuspected clinically.

Cancer of the Major Salivary Glands

Cancer of the major salivary glands is not uncommon. Tumors occur most frequently in the parotid gland (about 85%), less often in the submaxillary (15%), and very rarely in the sublingual gland. Most benign mixed tumors of the salivary gland have a tendency toward malignant degeneration. In the parotid gland about 25% of all tumors are malignant, whereas in the submaxillary gland about 75% are malignant.[1]

The symptom first noted by the patient is almost invariably a lump in the parotid or submaxillary region. In the majority of cases the patient has been aware of an abnormality for many months or even years before medical advice is sought. When the seventh nerve is compressed or actually infiltrated by the parotid tumor, with resulting facial paralysis, the growth in most cases is relatively far advanced or recurrent. The submaxillary gland is closely associated with the lingual branch of the trigeminal nerve (sensory), so that pain is often a predominant early symptom, especially in invasive malignant growth.

In general, the treatment of salivary gland tumor is surgical, as these tumors are generally not radiosensitive. Since these tumors tend to become malignant, they should all be excised. The question of neck dissection at the time of removal of the parotid tumor must be determined on the basis of the morbid anatomy and histologic character of the growth. If a submaxillary gland tumor is malignant, block dissection of the neck should be done at that time.

Patients do not die of benign mixed tumors of the major salivary gland,

and almost all cases can be cured by adequate surgical excision. In tumors regarded as malignant by the pathologist, a 40% to 50% five-year "cure rate" has been obtained. The most important danger of incomplete removal is the possibility of a recurrence of malignancy.

When surgery cannot be done, radiation should be tried.

Cervical Masses

Exclusive of goiter, most persistent lumps of the neck are malignant neoplastic disease, most malignant tumors of the neck are metastatic, and most malignant tumors of the neck come from primary sites in the head and neck area. From 1950 to 1955, 1,216 patients with a mass in the neck as a primary or dominant finding were admitted to the Illinois Research Hospital.[23] Neoplastic disease (including lymphomas) accounted for over 50% of the cervical masses. If benign thyroid disease was eliminated, the percentage of neoplastic disease problems rose to nearly 80%. Only 6.6% were inflammatory. Of 413 metastatic malignant tumors, 328 were metastatic from above the clavicle and 35 from below the clavicle.

Medical Treatment

Relief of pain, maintenance of nutrition, and prevention and treatment of respiratory and vascular complications are all within the realm of the internist. Although the incidence of radiation necrosis is low, the discomfort and pain resulting from this complication are marked, and characteristically, radiation necrosis is painful and tender. When radiation necrosis occurs in the mouth, warm gargles and local anesthetics are of value. If the pain is severe and limited to the distribution of the fifth nerve, alcohol injection or section of the sensory root (in the more prolonged cases) often gives dramatic relief. Narcotics should be reserved but, when used, should be used in adequate doses. Local use of soluble corticoids or systemic corticoids may produce dramatic relief of the inflammatory symptoms.

The maintenance of nutrition may be a major problem. Liquids are handled more easily than are semisolid or solid foods, and thus high caloric liquids supplemented with vitamins are often used. During the acute period of radiation reactions it is most important to maintain the liquid intake. Mead-Johnson feeding tubes are of value in the more severe nutritional problems. One patient whom we have recently seen has had a tube for two years, the tube being changed about once a month. Gastrostomy is rarely necessary.

Activated zinc peroxide or other local antiseptics are used for localized radionecrosis. The activated zinc peroxide is made up into a paste and applied every three hours by means of gauze and a tongue spatula. In the more severe cases, where trismus, pain and tenderness are present, there is frequently underlying infection, and broad-spectrum antibiotics are indicated.

Bronchopneumonia is a serious complication. The same principles are applicable in its prevention as are applicable in any debilitated patient. When there is a question as to whether a tracheotomy is necessary, it is probably wiser to perform one.

Vascular complications are unusual. One occasional complication of a bilateral neck dissection and jugular vein ligation is the occurrence of increased intracranial pressure, due to poor collateral circulation and drainage. The immediate treatment is similar to the treatment of any increased intracranial pressure. We have used large doses of prednisolone, with apparent success, in such a patient.[24] Surgical decompression is rarely required. The collateral circulation usually develops over a period of months, with gradual diminution in the cerebral edema.

Chemotherapy for metastatic or inoperable head and neck cancer is generally disappointing. Chemosurgery may be of value in inoperable cases. Estrogens have been used in advanced salivary gland tumors, with report of regression.[25] Further evaluation of this interesting form of therapy is necessary.

Summario in Interlingua

Iste articulo esseva scribite pro le internista. Illo ha le objectivo de passar in revista un numero de factores importante in le precoce diagnose e tractamento de cancere del capite e del collo.

Cancere oral representa plus que 5% de omne formas de cancere human. In circa 90% del casos de cancere oral il se tracta de carcinomas epidermoide. Le majoritate de illos es ben differentiate. Le plus maligne e le non-differentiate varietates ha un affinitate pro le structuras in le parte posterior del cavitate oral.

Inter le factores que determina le prognose de cancere oral, le plus importante es le promptitate del diagnose. Il es generalmente acceptate que irradiation es le therapia de election pro lesiones in le parte posterior del cavitate oral. Lesiones del tertio posterior del base lingual—in tanto que illos es ben lateralisate e micre—pote esser excidite chirurgicamente. Lesiones in le dorso e le parte intermediari del lingua es usualmente attaccate per radiation. Del altere latere, il existe considerabile differentias de opinion in re le tractamento de election pro tumores in le aspectos plus anterior del cavitate oral.

Varie centros cancerotherapeutic reporta pro tumores nasopharyngee un frequentia de 0,5 a 1% de omne casos de cancere. Lymphosarcomas, lympho-epitheliomas, e non-differentiate carcinomas epidermoide es le commun tumores nasopharyngee. Le prompte diagnose depende de caute examines nasopharyngee in omne patientes con persistente symptomas referibile al aure medie e al passages nasal e in patientes con allargamentos cervical. Le examine debe includer un examine digital e un indirecte vista de speculo per rhinoscopia posterior. Roentgenotherapia externe es le tractamento de election.

Le ver incidentia de carcinoma del larynge es impossibile a determinar a causa del marcate confusion de classification, sed il es probabile que illo representa circa 3% de omne formas de cancere. Un del plus importante causas del disfavorabile prognose in certe formas de cancere del larynge es le retardo inter le declaration del symptomas e le establimento del diagnose. Raucitate del voce que persiste durante plus que tres septimanas debe esser considerate como suspecte. Radiation e chirurgia es ambes importante in le tractamento de carcinoma laryngee. In casos in que laryn-

gectomia total es requirite, dissection prophylactic del collo es recommendate a causa del resultante augmento de "curationes," del plus alte numero de nodos positive que es trovate al operation post que illos habeva escappate al examine clinic, e del facto que le metastases cervical es usualmente unilateral.

Cancere del major glandulas salivari non es incommun. In general, le tractamento es chirurgic, proque tal tumores es usualmente non radio-sensibile.

A parte le occurrentia de struma, le majoritate del casos de massas persistente in le collo es causate per un maligne morbo neoplastic. Le majoritate del tumores maligne es metastatic. E le majoritate del maligne tumores del collo resulta ab sitos primari in le area del capite e del collo.

BIBLIOGRAPHY

1. Martin, H.: Cancer of the head and neck. A monograph for the physician, 1949, American Cancer Society, Inc. of New York, New York.
2. Ackerman, L. V., and del Regato, J. A.: Cancer of the respiratory system and upper digestive tract, *in* Textbook of cancer, 1954, The C. V. Mosby Company, St. Louis, pp. 198–475.
3. Mills, C. A., and Porter, M. M.: Tobacco smoking and cancer of the mouth and respiratory system, Cancer Research **10**: 539–542, 1950.
4. Paymaster, J. C.: Cancer of the buccal mucosa. A clinical study of 650 cases in Indian patients, Cancer **9**: 431–435, 1956.
5. Ahlbom, H. E.: Simple achlorhydric anemia, Plummer-Vinson syndrome, and carcinoma of the mouth, pharynx and oesophagus in women, Brit. M. J. **2**: 331–333, 1936.
6. Ward, G. E., and Hendrick, J. W.: Benign tumors and premalignant lesions of the oral cavity, *in* Textbook on tumors of the head and neck, 1950, The Williams and Wilkins Company, Baltimore, pp. 211–241.
7. Berridge, J., and James, A. G.: The management of lingual cancer, Surg., Gynec. and Obst. **103**: 595–606, 1956.
8. Ash, C. L., and Millar, O. B.: Radiotherapy of cancer of the tongue and floor of the mouth, Am. J. Roentgenol. **73**: 611–619, 1955.
9. Modlin, J., and Johnson, R. E.: The surgical treatment of cancer of the buccal mucosa and lower gingiva, Am. J. Roentgenol. **73**: 620–627, 1955.
10. Lampe, I.: Radiation therapy of cancer of the buccal mucosa and lower gingiva, Am. J. Roentgenol. **73**: 628–635, 1955.
11. Discussion of Symposium on Treatment of Cancer of the Oral Cavity, Am. J. Roentgenol. **73**: 635–638, 1955.
12. Slaughter, D. P.: Surgical management of intraoral cancer, Am. J. Roentgenol. **73**: 605–610, 1955.
13. Ackerman, L. V., and del Regato, J. A.: Radiotherapy of cancer, *in* Textbook of cancer, 1954, The C. V. Mosby Company, St. Louis, pp. 99–142.
14. Garland, L. H.: Applied radiation therapy *in* The physiopathology of cancer, edited by Homburger, F., and Fishman, W. H., 1953, Hoeber-Harper, New York, pp. 949–998.
15. Curry, L. T., and Friedberg, S. A.: Diagnosis and treatment of malignancies of the nasopharynx, S. Clin. North America **20**: 153–161, 1940.
16. Sooy, F. A.: Experimental treatment of recurrent carcinoma of the nasopharynx with electrodesiccation, radioactive cobalt and x-ray radiation, Ann. Otol., Rhin. and Laryng. **65**: 723–735, 1956.
17. Lindsay, J. R., and Ironside, W. M. S.: Carcinoma of larynx, classification and results of treatment, Laryngoscope **65**: 1117–1128, 1955.
18. Friedberg, S. A., and Wallner, L. J.: Selected problems in the diagnosis of laryngeal carcinoma, Arch. Otolaryng. **58**: 521–535, 1953.
19. Wallner, L. J.: Smoker's larynx, Laryngoscope **64**: 259–270, 1954.

20. Ogura, J. H.: Surgical pathology of cancer of the larynx, Laryngoscope **65**: 867–926, 1955.
21. Kuhn, A. J., Devine, K. D., and McDonald, J. R.: Cervical metastases from squamous cell carcinoma of the larynx, Laryngoscope **67**: 169–190, 1957.
22. Leroux-Robert, J.: Indications for radical surgery, partial surgery, radiotherapy and combined surgery, and radiotherapy for cancer of the pharynx and hypopharynx, Ann. Otol., Rhin. and Laryng. **65**: 137–153, 1956.
23. Slaughter, D. P., Majarakis, J. D., and Southwick, H. W.: Clinical evaluation of swellings in the neck, S. Clin. North America **36**: 3–90, 1956.
24. Kofman, S., Garvin, J. S., Nagamani, D., and Taylor, S. G., III: Treatment of cerebral metastases from breast carcinoma with prednisolone, J. A. M. A. **163**: 1473–1476 (Apr. 20) 1957.
25. White, G., and Garcelon, G. G.: Estrogen therapy in advanced malignant salivary gland tumors, New England J. Med. **253**: 410–412, 1955.

INCIDENCE OF THYROTOXICOSIS AMONG REFUGEES FROM NAZI PRISON CAMPS *

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THIS report represents a three-year (1951 to 1954) study of the incidence of thyrotoxicosis among refugee as against nonrefugee patients referred to the Thyroid Clinic, Cedars of Lebanon Hospital, Los Angeles, with a comparison study of refugee and nonrefugee patients registered in the General Outpatient Clinic.

The study was stimulated by the impression that there was a high incidence of thyrotoxicosis among patients who were refugees from Nazi prison camps. The histories of these patients were more or less similar in pattern. They had all spent up to four years in the prison camps. Their lives just prior to, during and after internment were characterized by horrendous experiences and marked suffering, both physical and mental. They had been subjected to inhuman treatment themselves, and had been eye witnesses to the inhuman treatment of others. Added to this were untold hardships encountered after escape or release from camps, during flight from one inhospitable country to another. Even their arrival in the United States did not put an end to their apprehension and hardships. They encountered difficulties in adjusting to a new environment, a different language and, in most cases, another means of earning a livelihood.

This group, all of whom had been inmates of Nazi prison camps, came from average German communities, and had been subjected to uncommonly severe stress for long periods of time, appeared to be excellent subjects for comparison with our Los Angeles patients for studies relating emotional stress to the incidence of thyrotoxic disturbances.

During the period of study a total of 256 patients were referred to the Thyroid Clinic. Sixty-three (24.6%) of this group were refugees, and 193 (75.4%) were nonrefugees. The specific diagnoses and the number of refugees and nonrefugees in each group are presented in table 1. The total number of patients registered in the General Out-patient Clinic was 5,155, of whom 4,554 (86.8%) were nonrefugees and 601 (13.2%) were refugees (table 2).

Toxic goiter (Graves' disease) was diagnosed in 63 patients, 23 (36.5%) of whom were refugees (table 3.) The ratio of refugees to nonrefugees in this group is particularly significant when we note that the refugee group constituted only 13.2% of the total clinic population; the incidence is more than three times that found in the nonrefugee group.

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TABLE 1

Diagnoses and Incidence among Thyroid Clinic Cases

Diagnosis	Total No. of Cases*	No. of Refugee Cases
Euthyroid	35	6
Probable euthyroid†	23	5
Nodular goiter, in euthyroid cases	80	20
Toxic goiter (hyperthyroidism; Graves' disease)	63	23
Definite toxic nodular goiter	14	3
Questionable toxicity (nodular goiter)	18	4
Thyroiditis	6	0
Hypothyroid (postoperative and spontaneous)	12	1
Adenocarcinoma	5	1
Totals	256	63

* Refugee and nonrefugee.
† Insufficient data.

Similar ratios occurred in the groups with (1) combined Graves' disease and toxic nodular goiter, and (2) combined Graves' disease, toxic nodular goiter and questionable toxic goiter with ratios based on a 10,000 population for each group, refugee and nonrefugee, the ratios become even more significant (table 4).

TABLE 2

General Clinic Cases Reviewed

Total number	5,155	
Refugees	601	13.2%
Natives (or nonrefugees)	4,554	86.8%

DISCUSSION

Many persons are subjected to emotional stress, yet only a few develop thyrotoxicosis. Psychosomatic studies have shown that the factors that determine whether a particular person will develop thyrotoxicosis, or some other disease or malfunction, are (1) inherent constitutional make-up ("Gestalt" [7]), and (2) severity and duration of emotional stress.[1-8] Theoretically, everyone has his own breaking point; the severity and duration of

TABLE 3

Incidence of Toxic Goiter

	Total No. of Cases	Nonrefugees	Refugees	Percentage of Refugees
Hyperthyroidism (Graves' disease)	63	40	23*	36.5
Toxic nodular goiter	14	11	3	20.0
Subtotals	77	51	25	33.7
Questionable toxic goiter	18	14	4	22.2
Totals	95	65	29	31.6

* This group consisted of 17 women, with ages ranging between 27 and 72 years (average, 48.0 years), and six men, with ages ranging between 41 and 69 years (average, 57.5 years).

TABLE 4

Incidence of Thyroid Disease; Rate per 10,000 Population (in Respective Groups)

Grouped diagnoses	Nonrefugees	Refugees	Ratio of Refugees to Nonrefugees
Hyperthyroidism	88	382	4.3:1
Hyperthyroidism Toxic nodular goiter	112	402	3.6:1
Hyperthyroidism Toxic nodular goiter Questionable toxic goiter	143	499	3.5:1

stress that can be tolerated varies from individual to individual. When the threshold of tolerance is reached, some clinical syndrome, such as gastrointestinal dysfunction, cardiovascular disorders, mental aberration or thyrotoxicosis, will be manifested (figure 1).

This was well demonstrated during World War II, with development in servicemen of pathologic syndromes directly attributable to emotional stress and closely related to the degree of situational tension. Disturbed physiologic conditions were manifested at the induction center, became more evident as the servicemen came closer to the port of embarkation, and increased in severity and number as they neared the combat areas. The variation from individual to individual was further demonstrated during combat, when even servicemen with great resistance to the effects of emotional stress developed functional disturbances of one type or another. Some soldiers

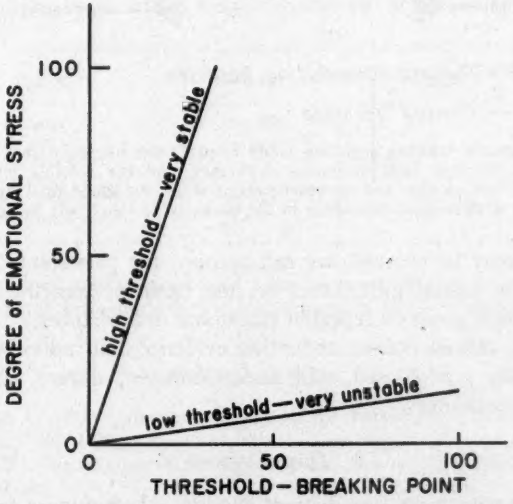

FIG. 1. Showing the relationship of emotional stress and threshold or breaking point when abnormal symptoms may appear.

broke down early in battle, and some only after being under constant fire for days (figure 2).

The factors that determine the point of breakdown—(1) severity and duration of emotional stress, and (2) inherent make-up—were pointed out by Cannon [2] some 40 years ago: "If we conceive the organs disturbed in emotional stress as being protected from rude disturbance by a high neurone threshold, requiring great excitation in the central nervous system before

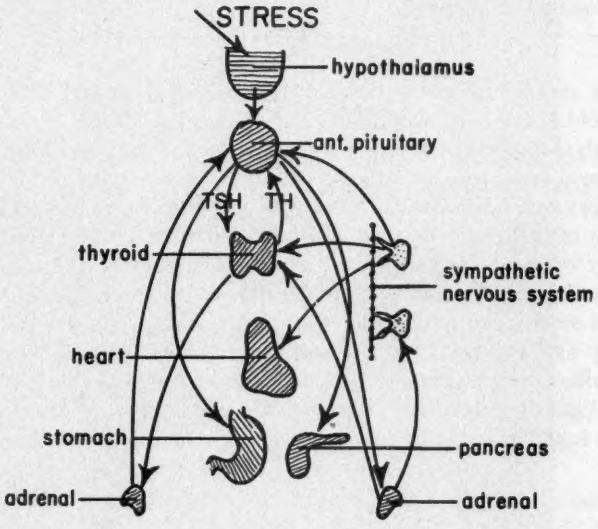

FIG. 2. Schematic drawing depicting (only in part) the interrelationship of the various endocrine glands, through their producing hormones, and the possible physiologic effects they may have on one another and on other organs when one gland or a group of glands is overstimulated, is weaker than the others in the chain, or is inherently more sensitive.

the threshold may be crossed, we can account for persistent disturbance of these organs in pathological cases on the basis of wearing down of the threshold through great or repeated emotional disturbances."

These observations constitute further evidence that individuals, especially those genetically predisposed, will under sufficient duress manifest pathophysiologic disturbances.[9, 10, 11]

CONCLUSION

This study comprises two distinct groups: (1) refugees from Germany, who had been confined to Nazi prison camps for periods up to four years,

with more or less similar experiences, characterized by severe physical and emotional stress, and (2) the total patient population registered in a free clinic in an average large American city (Los Angeles). The incidence of thyrotoxicosis in the refugee group was almost four times that found in the nonrefugee group. These observations lend support to the long-held view that emotional stress is an important contributing factor to the development of thyrotoxicosis.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Durante le triennio de 1951 a 1954, 24,6% del patientes presentate al Clinica Thyroide del Hospital "Cedars of Lebanon" a Los Angeles in California esseva exprisioneros de campos de concentration nazi. Durante le mesme periodo, solmente 13,2% (601) del total numero (5.155) de patientes visitante in omne le clinicas de iste hospital esseva refugiatos.

Inter le 256 patientes presentate al Clinica Thyroide, 63 (24,6%) esseva considerate como suffrente de toxic struma nodular, e 23 (36,5%) de iste 63 esseva refugiatos. Assi le incidentia de toxic struma nodular esseva tres vices plus alte inter refugiatos que inter non-refugiatos. Simile proportiones esseva notate pro (1) le combination de morbo de Graves con toxic struma nodular e (2) le combination de morbo de Graves con toxic struma nodular e dubitose struma toxic.

Le incidentia del morbos thyroide deveni ancora plus frappante quando illo es exprimite super le base de un population de 10.000. Vide le tabula sequente:

INCIDENTIA DE MORBO THYROIDE PRO 10.000

Gruppo Diagnostic	Non-Refugiatos	Refugiatos	Proportion de Refugiatos a Alteres
Hyperthyroidismo	88	382	4,3 : 1
Hyperthyroidismo Toxic Struma Nodular	112	402	3,6 : 1
Hyperthyroidismo Toxic Struma Nodular Dubitose Struma Toxic	143	499	3,5 : 1

Iste observationes presta supporto al vista, acceptate depost longe tempore, que stress emotional es un importante factor contributori in le disveloppamento de thyrotoxicosis.

BIBLIOGRAPHY

1. Cannon, W. B.: Conditions affecting secretion of the thyroid gland, Boston M. and S. J. 75: 562 (Oct. 19) 1916.
2. Plummer, H. S.: The function of the thyroid gland, Beaumont Foundation, 1925, C. V. Mosby, St. Louis.
3. Bram, I.: Psychic trauma in pathogenesis of exophthalmic goiter, Endocrinology 11: 106, 1927.

4. Moschcowitz, E.: The nature of Graves' disease, Arch. Int. Med. **46**: 610, 1930.
5. Goodall, J. S., and Rogers, L.: The effects of emotions in the production of thyrotoxicosis, M. J. and Rec. **138**: 411, 1944.
6. Means, J. H.: The function of the thyroid gland, Beaumont Lecture, 1948, Charles C Thomas, Springfield, Illinois.
7. Ham, G. C., Alexander, F., and Carmichael, H. T.: A psychosomatic theory of thyrotoxicosis, Psychosom. Med. **13**: 18, 1951.
8. Lidz, T.: Emotional factors in the etiology of hyperthyroidism, Psychosom. Med. **11**: 2, 1949.
9. Pauling, L., Itano, H. A., Singer, S. J., and Wells, I. C.: Sickle cell anemia, a molecular disease, Science **110**: 543, 1949.
10. Pauling, L.: The nature of molecular diseases, presented before the 37th Annual Session of the American College of Physicians, April 18, 1956, Los Angeles, California.
11. Neel, J. V.: Human hemoglobin types, their epidemiologic implications, New England J. Med. **256**: 161 (Jan. 24) 1957.

THE PLASMA INSULIN-I^{131} IN DIABETIC PATIENTS *

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Clinical classifications of diabetes generally divide the disease into two or three categories. The difference between the adult and the juvenile types of diabetes has long been recognized, and is based not only on age of onset but also on other clinical features. The important characteristics of the juvenile group are weight loss and ketosis occurring in the absence of adequate insulin therapy, and a dependence on exogenous insulin. Diabetic patients who have experienced the onset of the disease during adulthood tend to fall into two rather distinct groups, one characterized by a dependence on exogenous insulin, required to maintain weight and prevent ketosis, and the other characterized by obesity and a lack of dependence on exogenous insulin. Lawrence [1, 2] describes three types of diabetes: lipoplethoric, lipo-atrophic, and insulin-deficient. Himsworth [3] has divided diabetic subjects into insulin-sensitive and insulin-insensitive types, based on the response of the blood sugar to a glucose-insulin tolerance test. Ricketts [4] has reported that the insulin requirement in depancreatized patients is only about 40 units per day, yet many diabetics may require larger doses. In each of these classifications there is implied some abnormality of insulin metabolism, and studies with labeled insulin should give some insight into this matter.

Evidence that insulin labeled with I^{131} behaves in the body precisely as does the original insulin is only indirect. Ferrebee, Johnson, Mithoefer and Gardella [5] demonstrated a comparable hypoglycemic effect of insulin after iodination. In the authors' laboratory, with the rabbit as a test animal, a slight diminution was noted in the hypoglycemic activity of iodinated insulin. It should be emphasized, however, that only a small percentage of the insulin tyrosine molecules are iodinated in the labeling process, and it is doubtful that the standard method of insulin assay is sensitive enough to show the slight losses of activity that might be occasioned by iodinating only a few of the molecules. Thus the possibility must be kept in mind that none of the labeled molecules has insulin effect. Jensen [6] has shown an irreversible loss of hypoglycemic activity in heavily iodinated insulin. Furthermore, Berson, Yalow, Bauman, Rothschild and Newerly [7] have demonstrated the appearance of I^{131} in other electrophoretic fractions of the serum proteins

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after the administration of insulin-I^{131} although the mechanism of a transfer of I^{131} from insulin to a serum protein remains obscure.

Although the perfect experiment has not yet been devised which will show conclusively that labeled insulin molecules behave exactly as does insulin, the bulk of the evidence to date is in favor of this. This paper presents the data on the disappearance of labeled insulin from the plasma in various types of diabetic subjects.

Methods

Insulin was labeled with I^{131} by direct iodination, as described by Ferrebee et al.[5] The studies were carried out on fasting subjects who had received no insulin for at least 24 hours prior to the test. Each patient was injected intravenously with 3.0 units of the labeled insulin per M^2 body surface. Blood

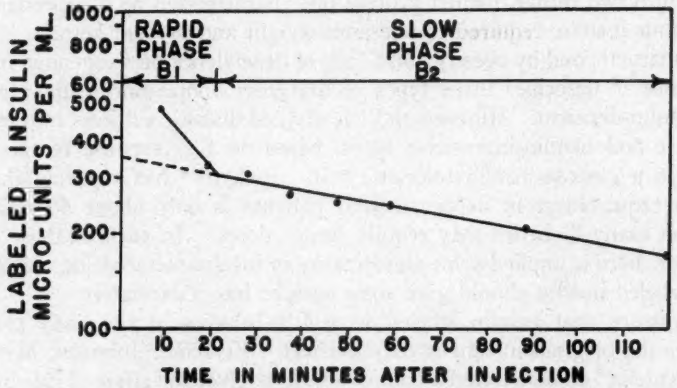

Fig. 1. Logarithmic plot of the disappearance of labeled insulin from the plasma of case 3 showing the two different phases. The dotted line represents the extrapolation to the zero time for the second phase.

samples were taken at intervals of from 10 to 20 minutes for the succeeding one or two hours. Zinc hydroxide precipitates of the serum were prepared according to the method of Barker, Humphrey and Soley.[8] After the precipitates had been washed three times with water, the residues were prepared for assay of radioactivity by dissolving in NaOH and drying in small glass dishes. Assay for radioactivity was carried out in an end-window Geiger counter. Appropriate corrections were made for decay and self-absorption and the result expressed as micro-units of labeled insulin per milliliter of serum. Although, as pointed out above, a small portion of the serum precipitable radioactivity may belong to proteins other than insulin, the use of such a unit is convenient as long as the limitations are remembered.

The patients selected for this study were as follows: Group I, normal individuals; Group II, obese diabetics, not dependent upon insulin; Group III, diabetics, adult, with onset of the disease between the ages of 20 to 40

years, dependent on insulin for maintenance of weight but with no history of an acidosis; Group IV, diabetics dependent upon insulin for maintenance of weight, with a history of one or more serious incidents of acidosis and with the onset of disease in childhood or adolescence.

Results

The plasma concentration of labeled insulin is expressed as a logarithm. In man the plasma disappearance curve for the labeled insulin consists of an initial rapid phase, followed by a slower second phase, and is similar in form to that described for the dog.[9] This form for the disappearance curve is found for all of the groups and a typical example is shown in figure 1. The initial rapid phase is completed about 15 minutes after injection of the labeled material. Analysis of the variance shows * that the second phase of disappearance follows a first-order relationship, such that,

$$\log Y = A + B_2X,$$

where Y is the serum concentration of labeled insulin expressed in micro-units per milliliter and X is the time after injection in minutes. In such a relationship the constant A is the logarithm of the insulin concentration at zero time, while B_2 is a rate constant that is characteristic of the disappearance rate during the slow second phase. The slope B_2 is determined in each case from the logarithmic plot of the data by the method of least squares, and values for this constant are shown in table 1. When the slopes for the initial phase (B_1) are compared with those for the second phase (B_2), initial phase slopes are significantly faster than are the second phase slopes (table 1). This initial phase is difficult to study in patients because of the necessity of obtaining multiple blood samples in rapid order. However, the rate of disappearance in the rapid phase largely determines the labeled insulin level for the early phases of the second phase of the curve. The point of intersection of the two parts of the curve would logically be the point of most significance in assessing the rapidity of the first phase, but since this point is not readily determinable, the theoretic starting point for the slow phase of the curve (A) may be taken as an indirect measure of the rapidity of the early phase. This assumption is reasonable only because the second phase slope is so much slower than is the first phase.

* Analysis of the variance of the logarithms of the insulin concentration:

Source of the Variance	Sum Squares	Degrees Freedom	Variance	F	P
Due to regression	2.288513	26	.088019		
Deviation from line of regression	1.196952	126	.009499	9.265	.001
Deviation of the means from regression	(0.972159)	(76)			
Replication	(0.224793)	(50)	.004495		
Total	3.485466	152			

Disappearance Rate

The values for the disappearance constant B_2 vary widely within the normal group, so that there is no significant difference between normals and abnormals (table 1). Therefore, this constant cannot be considered to be a characteristic of any clinical grouping for diabetes.

Initial Concentration

The values for A (the extrapolated value of the logarithm of the concentration of the labeled material at time zero) are shown in table 1. Group II (obese) diabetics show a significantly lower value for this constant ($P < .01$) than do either the normals or the other two groups of diabetics.

Table 1

Plasma Levels of Insulin-I^{131}
Logarithm of the plasma insulin-I^{131} concentration in micro-units per milliliter at time indicated

Case	10′	20′	30′	40′	50′	60′	90′	120′	B_1*	B_2	A	S
						Group I. Normal						
5	3.0061	2.8721	2.8360	2.7760	2.6391	2.5420	2.4281	2.4740	−.01340	−.00304	2.8296	±.1325
32		2.6220		2.5530		2.1109		1.5561		−.00705	2.7131	±.2261
		2.6339		2.5941		2.1109		2.1400				
38		2.6200		2.5142		2.4360		2.0300		−.00540	2.7470	±.0390
		2.6200		2.5600		2.4580		2.1461				
42		2.9420		2.8710		2.8645		2.7040		−.00228	2.9829	±.0121
		2.9489		2.8875		2.8340		2.7170				
43		2.9478		2.8980		2.7702		2.6780		−.00261	2.9796	±.0477
		2.9621		2.8980		2.7402		2.6900				
44		2.9225		2.8322		2.8005		2.7075		−.00205	2.9415	+.0154
		2.8980		2.8721		2.8239		2.6910				
Mean										−.00376	2.8656	
S.E.										±.00082	±0.0487	
						Group II. Obese Diabetics						
2	2.5841	2.4600	2.3250	2.2410	2.1524	2.1079	2.2410	2.0041	−.01241	−.00183	2.3258	±.1243
4	2.7410	2.6320	2.5928	2.3250	2.1439	2.2945	1.9341	2.3250	−.01090	−.00388	2.5479	±.1849
13	2.7802	2.5220	2.5821	2.4941	2.4360	2.4061	2.2580	1.9300	−.02582	−.00589	2.7199	±.0705
19	2.6700	2.5160	2.4490	2.3381	2.2998	2.2330	2.1619	1.9922	−.01540	−.00474	2.5601	±.0515
24		2.5728		2.4895		2.4784				−.00295	2.6259	±.0298
		2.5980		2.4529		2.4560						
Mean										−.00386	2.5559	
S.E.										±.00070	±0.0659	
						Group III. Insulin Dependent Diabetics						
15		3.1699	3.0518	3.0021	2.9700	2.9621	2.8800	2.7902		−.00263	3.1204	±.0473
11	3.3120	3.2441	3.2578	3.1860	3.1541	3.1198		3.1700	−.00679	−.00051	3.2161	±.0441
27		2.8320		2.7180		2.6642				−.00408	2.8682	±.0173
		2.8491		2.7500		2.6901						
34		3.1600		3.0828		3.1101				−.00090	3.1562	±.0155
				3.1200		3.1101						
30		3.1683		3.1400		3.1500				−.00123	3.2123	±.0187
		3.2201		3.1600		3.1400						
40		2.7848		2.7458		2.6868		2.4442		−.00338	2.8789	±.0223
		2.8430		2.7172		2.6868		2.4960				
26		2.7289		2.6101		2.5980				−.00388	2.8097	±.0386
		2.7781		2.6121		2.5980						
Mean										−.00237	3.0374	
S.E.										±.00056	±0.0679	

TABLE 1—*Continued*

Plasma Levels of Insulin-I^{131}
Logarithm of the plasma insulin-I^{131} concentration in micro-units per milliliter at time indicated

Case	10′	20′	30′	40′	50′	60′	90′	120′	B_1*	B_2	A	S
Group IV. Insulin Dependent Diabetics-Acidosis Group												
29		2.9224		2.8193		2.7791				−.00429	3.0261	±.0425
		2.9083		2.8499		2.7780						
3	2.6820	2.5540	2.4941	2.4329	2.3980	2.3719	2.3250	2.2920	−.01280	−.00226	2.5419	±.0426
25		2.6023		2.6462		2.5725				−.00228	2.7018	±.0351
		2.7040		2.5890		2.5501						
6		2.6282	2.5061	2.4240	2.3521	2.2921	2.2528	2.2921		−.00282	2.5567	±.0856
16	3.0940	3.0681	2.9540	2.9110	2.9221	2.900	2.7679	2.8258	−.00252	−.00209	3.0291	±.0554
17	2.5840	2.5239	2.5190	2.4779	2.4601	2.4360	2.3820	2.3720	−.00501	−.00148	2.5394	±.0278
28		2.5720		2.3023		2.4624		2.2481		−.00315	2.5746	±.0893
				2.3881		2.4880		2.1121				
31		3.1683		3.0998		3.0520				−.00240	3.1580	−.0493
		3.0401		3.0520		2.9591						
Mean										−.00259	2.7659	
S.E.										±.00029	±0.0922	
Mean									−.01167	−.00304	2.8216	
S.E.									±.00227	±.00030	±0.0658	

* Abbreviations:

B_1—Slope of the first phase of disappearance, obtained from the logarithmic plot of the 10- and 20-minute plasma-labeled insulin levels.

B_2—Slope of the second phase of disappearance obtained by the method of least squares applied to the logarithms of the plasma insulin concentrations in the specimens obtained from 20 to 120 minutes after injection. $B_2 = \frac{\Sigma xy}{\Sigma x^2}$.

A—Zero time intercept obtained by extrapolation of the least squares line derived from the logarithms of the labeled insulin concentration in the specimens from 20 to 120 minutes after injection.

S—Standard error of the estimate for the second phase. $S = \sqrt{\frac{\Sigma y^2 - B_1 \Sigma xy}{N}}$.

S.E.—Standard error of the mean. $S.E. = \sqrt{\frac{\Sigma x^2}{N(N-1)}}$.

Groups III and IV diabetics show values for this constant that are both above and below the mean for the normal group.

The relation between the values for A and B_2 is shown in figure 2 for each of the groups. A significant ($P < .01$) negative correlation exists in Groups I and III between the values for these two constants. For the Group II patients a direct correlation is obtained which is only slightly significant ($P = .05$). For the patients of Group IV, the correlation is not significant.

BLOOD SUGAR

The mean values for the blood glucose in each group are shown in table 2, expressed as per cent of the fasting level. The 20-minute decline for all of the diabetic groups is significantly less than is that for the normal group; however, this may well be a function of higher fasting levels in the diabetic subjects. The form of the curve differs significantly between the groups, such that Group I and II patients show the most rapid return to the fasting levels, while the Group III and IV patients show a continuing decline at the end of an hour (figure 3). No correlation is noted between the rate of the decline in the blood sugar and either of the two constants, A or B_2.

Discussion

The factors which may be considered to be important in determining the characteristics of the disappearance curve of labeled insulin from the plasma are the size of the endogenous or unlabeled insulin pool, the degree of plasma binding of the insulin, the binding of insulin by the cells, and the degradation of insulin within the cells (table 3).

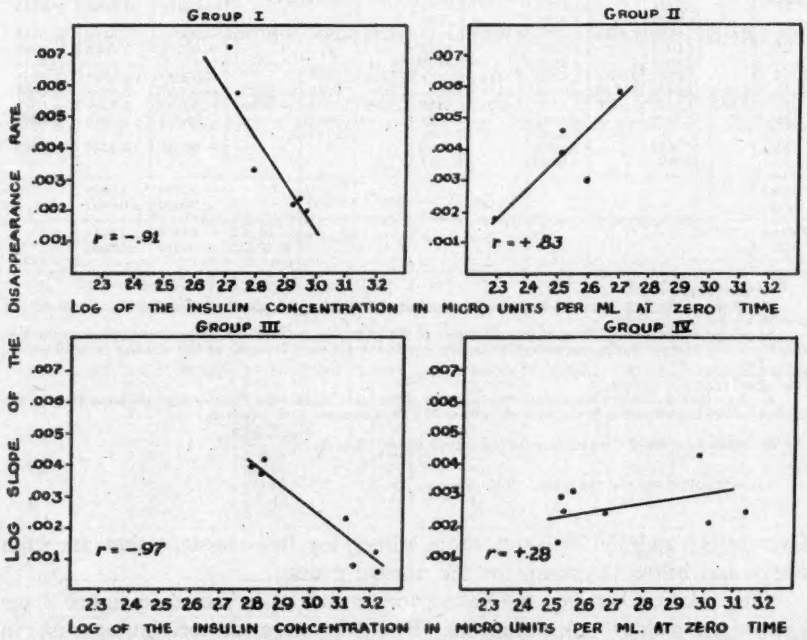

Fig. 2. The logarithm of the value for serum labeled insulin concentration at time zero (A) found by extrapolation of the second phase curve, is shown as the abscissa and the slope of the curve (B_2) is shown as the ordinate for each clinical group.

The size of the endogenous insulin pool is important but is not easily determinable. Methods for determining the insulin blood level have been reported by several authors,[10, 11, 12, 13] but the error inherent within these methods makes them of little use in determining the endogenous pool of insulin. From the theoretic standpoint, the size of the endogenous insulin pool must be known before the specific activity * of the tracer can be known. Strictly speaking, the disappearance constant for the labeled insulin cannot be considered as a measure of the actual disappearance of the endogenous insulin unless this specific activity can be known, since if a constant rate of disappearance of endogenous insulin is assumed, then for a small endo-

* Specific activity is defined as the ratio of labeled to unlabeled molecules of a given substance.

TABLE 2

Decrease in Blood Glucose after Labeled Insulin
Blood glucose expressed as per cent of the fasting level*

Group		20 Min.	30 Min.	60 Min.
I	Mean†	49	67	82
	S.E.*	9	15	8
	N	6	6	6
II	Mean	79	91	90
	S.E.	6	17	13
	N	5	5	5
III	Mean	81	73	74
	S.E.	3	5	6
	N	7	7	7
IV	Mean	78	65	62
	S.E.	8	9	9
	N	8	8	8

* Analysis of the variance of decrease in blood glucose.

Source	Degrees Freedom	Variance	F	P
Between groups	3	1,432	2.447	.05
Between times	2	85		
Within groups	66	585		
Interaction	6	2,483	4.244	<.01
Total	77	753		

† S.E.: Standard error of the mean.

genous insulin pool there would appear a high disappearance constant for any labeled insulin added to the system, whereas for a large endogenous pool and the same disappearance rate for endogenous insulin, there would appear a low disappearance constant for labeled insulin added. The error in as-

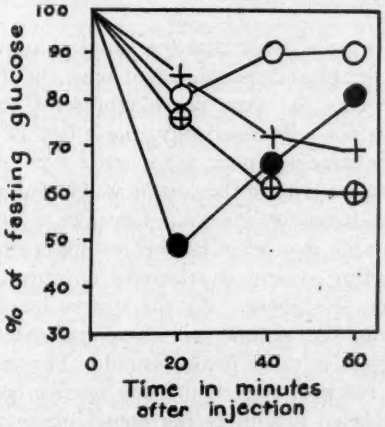

FIG. 3. Decline in the blood glucose expressed as per cent of the fasting level for each clinical group. Solid circles, Group I; open circles, Group II; crosses, Group III; crossed circles, Group IV.

suming that the disappearance rate for the labeled insulin is a measure of the disappearance rate for the endogenous insulin is small only if the amount of labeled insulin is large in comparison with the endogenous insulin pool. In these studies, however, the levels of labeled insulin were of the order of 200 to 2,000 micro-units per milliliter of serum, whereas the usual endogenous insulin levels are reported at from 2,000 to 5,000 micro-units per milliliter of serum.[11] From the selection of patients in this study, it can be expected that the variation in endogenous insulin pool is quite large, and this is no doubt one factor contributing to the great variation in the results.

Evidence in favor of plasma binding of insulin by the proteins has been presented by Welsh, Henley, Williams and Cox.[14] Differences were noted by these authors in the plasma binding of insulin dependent upon previous insulin medication, suggesting that saturation of the binding mechanism may play a role in determining the binding activity of the plasma for insulin at

TABLE 3

Theoretically Expected Effect of Various Factors on the Parameters of Labeled Insulin Disappearance from Plasma

Factor	Effect on A (Zero Time Concentration) of		Effect on B_2 (Disappearance Constant) of	
	Increased Factor	Decreased Factor	Increased Factor	Decreased Factor
Size of the endogenous insulin pool (unlabeled)	High	Low	Low	High
Saturation of the plasma insulin binding mechanism	Low	High	Low	Low
Tissue binding	Low	High	High	Low
Degradation	Low	High	High	Low

any given time. It is quite likely that the rapid phase of disappearance of labeled insulin from the plasma is coincident with the disappearance of the unbound insulin, whereas the slow phase represents the disappearance of the bound labeled insulin. Theoretically, the effect of plasma binding of labeled insulin can be quite complex, for even if a constant binding power is assumed, the binding activity of the plasma will be influenced by the degree of saturation with endogenous insulin. Consider a constant binding capacity for the plasma such that when labeled insulin is administered at a time when the plasma binding system is relatively unsaturated, the isotope will disappear slowly from this phase. As the system becomes more saturated with unlabeled insulin, the isotope will disappear more rapidly, since the added insulin is progressively less firmly bound. This increase will continue until a maximum is reached, after which the isotope becomes progressively diluted with the unlabeled insulin in the bound phase and the rate of disappearance of the isotope decreases. Thus, in table 3, low values are expected for B (disappearance constant for the slow phase) at the extremes

of either increased or decreased saturation of the binding mechanism, while the maximum could be found between these extremes.

The binding of insulin to the rat diaphragm, lactating mammary gland and adipose tissue has been established by Stadie, Haugaard and Vaughan [15] and by Hills and Stadie.[16] In the rat Haugaard, Vaughan, Haugaard and Stadie [9] found, after injection of labeled insulin, a high concentration of radioactivity in the liver and to a lesser extent in the skeletal muscle. Elgee, Williams and Lee [17] showed that this radioactivity could not be washed from the tissues, and considered this as evidence in favor of the binding of the hormone to the cell. Lee and Williams [18] showed the rapid uptake of labeled insulin within the liver cells, and demonstrated further that the labeled material was bound to the various intracellular components. This accumulation within the liver cell was rapid, such that 11% of the injected dose was found there in the first 15 minutes. It is probable that the initial rapid phase of plasma disappearance of labeled insulin, shown in figure 1, is coincident with the penetration of the insulin into the cells, with subsequent intracellular binding. That the processes of penetration and binding may be relatively independent of one another is suggested by the fact that lysed red cells combine with more insulin than do intact cells,[19] whereas liver homogenates combine with less hormone than do intact liver cells.[18] Evidently some limiting factor is present which brings the rapid initial disappearance of the insulin to an end, and it is possible that this occurs when an equilibrium is established between the binding capacity of the serum and that of the cell.

Very little is known about the actual degradation of insulin within the tissues and what influence this may have on the rate of disappearance of labeled insulin from the plasma. Various tissues possess the property of inactivating insulin, and liver tissue has been shown to be most active in this respect.[20, 21, 22] In the rabbit it has been shown that liver damage results in a decreased initial phase of plasma-labeled insulin disappearance.[23] This is consistent with the hypothesis that the rate of insulin disappearance during the early phase of the curve is in some way limited by liver function such that liver cell damage produces a slowing of the initial rapid phase.

The interpretation of the findings in the subjects of this study is difficult in view of the complexity of the factors outlined above; and the poor correlation between the clinical classification of diabetes and the alterations in disappearance characteristic of the labeled insulin becomes understandable. In the normal group a negative correlation is noted between A and B_2 (figure 2) which, from the theoretic standpoint, could be explained on the basis of normal variation in endogenous insulin pool, tissue binding, or degradation of insulin in the tissues. In the obese group (Group II), if an abnormally high rate of tissue degradation of insulin is assumed, the rapid disappearance of labeled material during the early phase can be explained. A sufficient endogenous insulin pool must be assumed such that the plasma binding sys-

tem is saturated enough that it will not retain large amounts of the labeled material in the circulation. This is consistent with some of the facts known about this type of diabetic, since normal or slightly lower than normal values for plasma insulin levels have been demonstrated in these patients.[11, 12] Consistent with this hypothesis is the form of the blood sugar curve after insulin (figure 3), which shows a rapid fall and a rapid return to the fasting level in both the normal group (Group I) and the obese group of diabetics (Group II). It is in these two groups that the plasma would be expected to be relatively saturated with insulin from endogenous sources such that added labeled insulin would remain largely unbound by the plasma and thus be readily available to the tissues where the hypoglycemic effect is initiated and quickly terminated. On the other hand, various degrees of unsaturation of the plasma would be expected to exist in the severe diabetics (Groups III and IV) such that added insulin would be quickly bound to the plasma and would exert its effect slowly. Such a response is noted in the blood sugar curve for these two groups where the level is still falling at the end of an hour.

In the nonobese adult diabetics (Group III), endogenous insulin levels have been shown to be low.[10, 12] In the severe juvenile diabetics (Group IV) these levels are found to be scattered widely (figure 2), and these variations might be explained on the basis of varying degrees of saturation of the unlabeled insulin pool which would be expected after a 24-hour withdrawal of insulin medication from patients who had been on relatively large doses.

From these studies it is obvious that caution must be exercised in applying the findings obtained from studies with labeled insulin to an interpretation of the clinical status of the diabetes.

Summary

1. Twenty diabetic subjects were classified clinically according to history of weight loss, response to insulin, and history of acidosis. Four groups were defined for this study: a normal group, a group of obese diabetics, a group of adult diabetics dependent upon insulin but without a history of acidosis, and a group of diabetics with onset during the growth period and with a history of acidosis.

2. The disappearance curve for insulin-I^{131} from the plasma was studied, and was found to consist of an initial rapid phase, completed in a few minutes, and a slower second phase following a logarithmic relationship. The two parameters of the disappearance during the slow phase were studied, using the extrapolated value for concentration at time zero as a measure of the distribution of the labeled insulin, and using the slope of this curve as a measure of the disappearance of the labeled material. Neither parameter alone was characteristic of any of the clinical groups, with the exception of the initial concentration of insulin for the obese group, which was significantly lower than that for the normal group.

3. The size of the unlabeled insulin pool in the body is not readily determinable but can affect the disappearance rate for the labeled insulin. For this reason, caution should be exercised in correlating data obtained from the use of labeled insulin with the clinical data.

Summario in Interlingua

Ab le puncto de vista clinic, le patientes diabetic se gruppa in plure categorias: Diabeticos juvenil con dependentia de insulina e le tendentia a cetosis, diabeticos adulte con dependentia de insulina e minus tendentia a cetosis, e diabeticos obese con nulle dependentia de insulina e absentia de cetosis. In un gruppo de 20 patientes, le tentativa esseva facite de correlationar le typo de diabete con le characteristicas del curva de disparition ab le plasma de insulina marcate con I^{131}. Sex subjectos normal esseva studiate pro objectivos de comparation. Esseva constatate que le materia radiomarcate e ligate a proteina dispareva ab le plasma in duo phases distincte: Un phase rapide initial que se completava in circa 10 a 20 minutas e un phase relentate que sequeva un relation logarithmic. Le constante de disparition durante le phase relentate esseva circa 0,7% del radio-material presente per minuta. Il non pareva que isto esseva specificamente characteristic de un del gruppos per contrasto con le alteres. Le extrapolation del curva de disparition ab le phase relentate usque al tempore zero resultava in valores que esseva significativemente plus basse pro le gruppo del diabeticos obese que pro le normales o le altere gruppos diabetic. Isto indicarea un plus basse concentration del marcate insulina in le plasma al comenciamento del phase relentate e se trova de accordo con un plus rapide disparition initial. Le sucro sanguinee in le normales e in le diabeticos obese monstrava un retorno rapide al valor del stato jejun post le injection de insulina, durante que illo del cetogene diabeticos juvenil e del typo adulte de diabetico monstrava un declino que continuava ancora al fin de un hora.

Le disparition ab le plasma de insulina radio-marcate es considerate como influentiate per un complexo de factores, incluse le dimension del reserva de insulina endogene, le grado de ligation plasmatic de insulina, le ligation de insulina intra le cellulas, e le degradation de insulina intra le cellulas. Il es probabile que le complexitate de iste factores explica le basse correlation del characteristicas del curva de disparition con le tableau clinic.

BIBLIOGRAPHY

1. Lawrence, R. D.: Types of human diabetes, Brit. M. J. **1**: 4703, 1951.
2. Lawrence, R. D.: Three types of human diabetes, Ann. Int. Med. **43**: 1199, 1955.
3. Himsworth, H. P.: The syndrome of diabetes mellitus and its causes, Lancet **1**: 465, 1949.
4. Ricketts, H. T., Brunschwig, A., and Knowlton, K.: Diabetes in totally depancreatized man, Proc. Soc. Exper. Biol. and Med. **58**: 254, 1945.
5. Ferrebee, J. W., Johnson, B. B., Mithoefer, J. C., and Gardella, J. W.: Insulin and adrenocorticotropin labeled with radioiodine, Endocrinology **48**: 277, 1951.
6. Jensen, H. F.: Insulin, 1938, Oxford University Press, London.
7. Berson, S. A., Yalow, R. S., Bauman, A., Rothschild, M. A., and Newerly, K.: Insulin-I^{131} metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin treated subjects, J. Clin. Investigation **35**: 170, 1956.
8. Barker, S. B., Humphrey, M. J., and Soley, M. H.: Clinical determination of protein bound iodine, J. Clin. Investigation **30**: 55, 1951.
9. Haugaard, N., Vaughan, M., Haugaard, E. S., and Stadie, W. C.: Studies of radioiodine labeled insulin, J. Biol. Chem. **208**: 549, 1954.

10. Bornstein, J., and Lawrence, R. D.: Plasma insulin in human diabetes mellitus, Brit. M. J. **2**: 1541, 1951.
11. Groen, J., Kamminga, C. E., Willebrands, A. F., and Blickman, J. R.: Evidence for the presence of insulin in blood serum. A method for approximate determination of insulin content of blood, J. Clin. Investigation **31**: 97, 1952.
12. Bornstein, J.: The insulin content of the blood plasma, Diabetes **2**: 23, 1953.
13. Vallance-Owen, J., Hurlock, B., and Please, N. W.: Plasma-insulin activity in diabetes, Brit. M. J. **2**: 583, 1955.
14. Welsh, G. W., Henley, E. D., Williams, R. H., and Cox, R. W.: Insulin-I^{131} metabolism in man, Am. J. Med. **21**: 324, 1956.
15. Stadie, W. C., Haugaard, N., and Vaughan, M.: Studies of insulin binding with isotopically labeled insulin, J. Biol. Chem. **199**: 729, 1952.
16. Hills, G., and Stadie, W. C.: The effect of combined insulin upon the metabolism of lactating mammary gland of the rat, J. Biol. Chem. **194**: 25, 1952.
17. Elgee, N. J., Williams, R. H., and Lee, N. D.: Distribution and degradation studies with insulin-I^{131}, J. Clin. Investigation **33**: 1252, 1954.
18. Lee, N. D., and Williams, R. H.: The intracellular location of labeled thyroxin and labeled insulin in mammalian liver, Endocrinology **54**: 5, 1954.
19. Haugaard, N., Haugaard, E. S., and Stadie, W. C.: Combination of insulin with cells, J. Biol. Chem. **211**: 289, 1954.
20. Mirsky, I. A., and Broh-Kahn, R. H.: The inactivation of insulin by tissue extracts. I. The distribution and properties of insulin inactivating extracts, Arch. Biochem. **20**: 1, 1949.
21. Broh-Kahn, R. H., and Mirsky, I. A.: The inactivation of insulin by tissue extracts. II. The effect of fasting on the insulinase content of the rat liver, Arch. Biochem. **20**: 10, 1949.
22. Mirsky, I. A., Perisutti, G., and Dixon, F. J.: The destruction of I^{131} labeled insulin by rat liver extracts, J. Biol. Chem. **214**: 397, 1955.
23. Bolinger, R. E., and Slinker, B. J.: Effect of carbon tetrachloride on distribution and disappearance of labeled insulin in rabbit serum, Proc. Soc. Exper. Biol. and Med. **88**: 574, 1955.

VITAMIN D INTOXICATION: REPORT OF TWO CASES TREATED WITH CORTISONE *

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EXCESSIVE vitamin D ingestion has been known since 1928 to produce toxic effects in humans.[1] Knowledge of these harmful effects has in recent years led physicians away from the use of large doses of this vitamin. The syndrome of vitamin D intoxication still occurs, however, and may present difficult diagnostic and therapeutic problems. Donegan et al.[2] reported two such cases from this institution in 1949. Two additional cases are reported here because of the gratifying response to cortisone therapy and because they manifest interesting features not sufficiently stressed in the existing literature.

CASE REPORTS

Case 1. This 71 year old white man had been well all of his life except for severe and progressive osteoarthritis of the hands and knees. Three weeks prior to admission he experienced the insidious development of weakness, polyuria, nocturia every 30 minutes, dry mouth, intense thirst, dysphagia, dysarthria, mental confusion, incoherence, somnolence and a staggering gait. A 30 pound weight loss was noted. It was learned several days after admission that he had been taking 200,000 units of vitamin D daily for one month prior to admission. He had been sold the vitamin D capsules containing 50,000 units each by his druggist without a prescription. With progression of the above symptoms he became disoriented, anorexic and severely dehydrated, and was admitted to Duke Hospital for evaluation and therapy on September 10, 1956.

Physical Examination: The patient was markedly dehydrated, semistuporous and completely disoriented, with fluctuating levels of consciousness. The blood pressure was 180/80 mm. of Hg; pulse rate, 64 per minute; respirations, 18 per minute; rectal temperature, 37.5° C. Skin turgor was decreased but there were no eruptions. There were no scleral or other abnormal calcifications. The tongue was dry and red but there was no atrophy of the papillae. Neck veins were flat in the supine position, and the lungs and heart were normal. The abdomen was flat, with normal bowel sounds. The liver, spleen and kidneys were not enlarged to palpation. The bladder was distended slightly above the pubis, and there was bilateral costovertebral angle tenderness. The prostate was hard and slightly enlarged, but no nodules were felt. Neurologic examination revealed symmetric hyperreflexia, bilateral extensor plantar reflexes and positive Chaddock's sign, but no localizing signs were elicited.

Laboratory and X-Ray Findings: The hemogram showed a hemoglobin of 13 gm. per 100 c.c.; white blood cell count, 9,600 per cubic millimeter, with 79% polymorphonuclears, 13% lymphocytes and 8% mononuclear cells. The urine showed 2 plus

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TABLE 1

Case 1, Pertinent Blood Chemical Findings

Day of Observation		1	4	9	22	26	37	74
Test Performed	Unit							
Calcium	Mg.%	13.5	14.5	15.1	11.0	10.1	9.8	9.0
Phosphorus	Mg.%	3.5	2.9	4.9	2.6	2.3	2.9	3.2
Potassium	mEq./L.	2.9	3.5	5.3	3.1	3.1	4.3	—
Chloride	mEq./L.	95.4	94.3	95	95	95.7	103	—
Sodium	mEq./L.	156.2	139.1	141	139.1	141.3	141.3	—
Nonprotein nitrogen	Mg.%	46	—	52	54	33	35	33
CO_2 combining power	mEq./L.	35.2	38.4	29.9	22.3	22.7	27	—

proteinuria and a strongly positive Sulkowitch's reaction. The urine sediment was loaded with white blood cells and gram-negative rods which were cultured and found to be Klebsiella organisms. Urine specific gravities ranged around 1.004 and were fixed below 1.010. Two hour excretion of phenolsulfonphthalein was 74%. Serologic tests for syphilis were negative, as was a stool guaiac test. An electrocardiogram showed changes of sinus bradycardia and left ventricular hypertrophy with broad u waves. A chest x-ray was normal, and x-rays of the skull, hands and spine showed only diffuse demineralization and osteoarthritis. Pertinent chemical findings are listed in table 1. Admission blood chemistries revealed a serum potassium of 2.9 mEq./L.; serum sodium, 156.2 mEq./L.; serum chloride, 95.4 mEq./L.; carbon dioxide combining power, 35.5 mEq./L.; nonprotein nitrogen, 46 mg. per 100 c.c.; serum calcium, 13.5 mg. per 100 c.c.; serum phosphorus, 3.5 mg. per 100 c.c.; alkaline phosphatase, 1.9 Bodansky units per 100 c.c.

Course in Hospital: The initial impression was toxic encephalopathy, and the etiology was established as vitamin D intoxication by the findings of hypercalcemia and normophosphatemia, and a history of excessive vitamin D ingestion. Cortisone was begun on the tenth hospital day in a dosage of 200 mg. per day. There was improvement in the sensorium in 48 hours, and return of serum calcium to normal levels in 13 days. The hypokalemic alkalosis persisted, and the patient continued to have copious urine outputs which exceeded fluid intake on several days. This led to more marked dehydration, and a transient hypotensive episode on the eighteenth hospital day, which was easily corrected by more careful attention to fluid and electrolyte balance. Fluids were forced, and the patient was given potassium supplements,

TABLE 2

Case 2, Pertinent Blood Chemical Findings

Day of Observation		2	13	19	30	50	70	100	220	450
Test Performed	Unit									
Calcium	Mg.%	14.4	13.3	14.9	13.6	9.7	9.7	9.3	9.8	—
Phosphorus	Mg.%	3.8	3.0	3.2	3.6	3.0	3.0	3.1	2.5	—
Potassium	mEq./L.	2.8	3.1	4.0	5.1	4.5	4.0	—	—	—
Chloride	mEq./L.	95.0	94.3	91.6	—	94.3	—	—	—	—
Sodium	mEq./L.	141.3	145.6	150	141.2	147.8	—	—	—	—
Nonprotein nitrogen	Mg.%	68	37	48	—	73	52	34	42	42
CO_2 combining power	mEq./L.	33.8	34.8	39.2	35.2	29.9	33.9	—	—	—

Achromycin, Mandelamine and Gelusil during the course of cortisone therapy. Because of obstructive uropathy from benign prostatic hypertrophy, an indwelling catheter was left in the bladder to ensure adequate urinary drainage. Six weeks after discharge he was re-admitted for transurethral resection of the prostate gland. He tolerated the procedure well and had no manifestations of residual vitamin D intoxication. (See table 1 for pertinent chemical data.)

Case 2. This 69 year old white female was transferred to Duke Hospital from another hospital on September 10, 1954, because of progressive weakness, depressive symptoms, and change in mental status of two weeks' duration. One month prior to admission a right nephrolithotomy had been performed elsewhere, with a benign postoperative course. The patient had done well until two weeks prior to admission, when she developed anorexia and became severely depressed and withdrawn. This was followed by nausea, vomiting, memory loss, disorientation, and finally unresponsiveness. Four days prior to admission she was admitted to another hospital, where

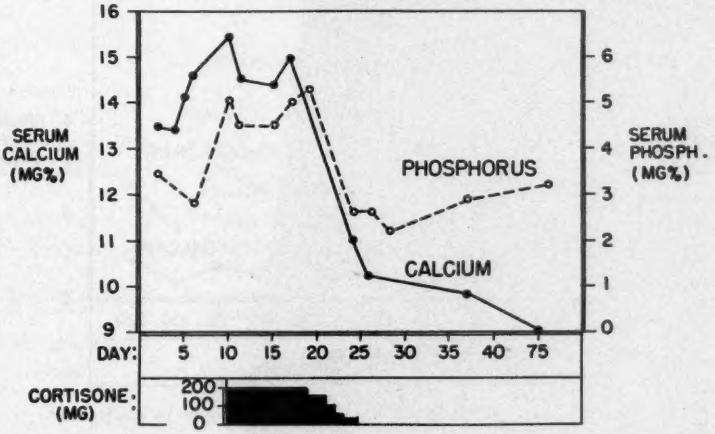

FIG. 1. *Case 1.* Serum calcium and phosphorus response to cortisone.

she was found to have elevation of the blood nonprotein nitrogen to 58 mg. per 100 c.c. She continued to have copious urine outputs despite poor fluid intake and obvious dehydration. At the time of transfer to Duke Hospital, no history could be obtained from her and the family knew nothing of any medications she had taken.

Physical Examination: The patient was a dehydrated, lethargic white woman who lay passively in bed with tears in her eyes. She appeared to hear when spoken to, but would not answer questions or follow commands. She would withdraw from noxious stimuli and would occasionally retch and vomit. The blood pressure was 170/70 mm. of Hg; pulse rate, 132 per minute; respirations, 14 per minute; oral temperature, 37° C. There were no corneal or other abnormal calcifications. The skin was dry, with decreased turgor. The tongue was red and dry, with no papillary atrophy. The lungs were normal, as was the heart except for sinus tachycardia and a grade II systolic precordial murmur. The abdomen was flat and soft, with well healed surgical scars in the right upper and lower quadrants. Bowel sounds were normal, and liver, spleen and kidneys were not palpable. There was no edema of the legs. Neurologic examination was normal except for symmetric hyperreflexia and the change in mental status noted above.

Laboratory and X-Ray Findings: The hemoglobin was 16.3 gm. per 100 c.c.; white blood cell count, 11,800 per cubic millimeter, with a normal differential count. Urine specific gravities were consistently low (in the range of 1.002 to 1.006). There was a faint trace of urine protein and a strongly positive Sulkowitch reaction. The urinary sediment showed 8 to 10 white blood cells and an occasional red blood cell per high power field. Admission blood chemical findings included a serum potassium of 2.8 mEq./L.; nonprotein nitrogen, 68 mg. per 100 c.c.; serum calcium, 14.4 mg. per 100 c.c.; serum phosphorus of 3.8 mg. per 100 c.c.; alkaline phosphatase, 1.3 Bodansky units per 100 c.c. The chest x-ray showed some old scarring of the right upper lung field. X-rays of the skull, spine and long bones showed only generalized diffuse demineralization and osteoarthritis. An electrocardiogram revealed changes suggesting left ventricular hypertrophy and prolongation of the Q-T interval to 0.53 second. Intravenous pyelograms were within normal limits. After the patient had

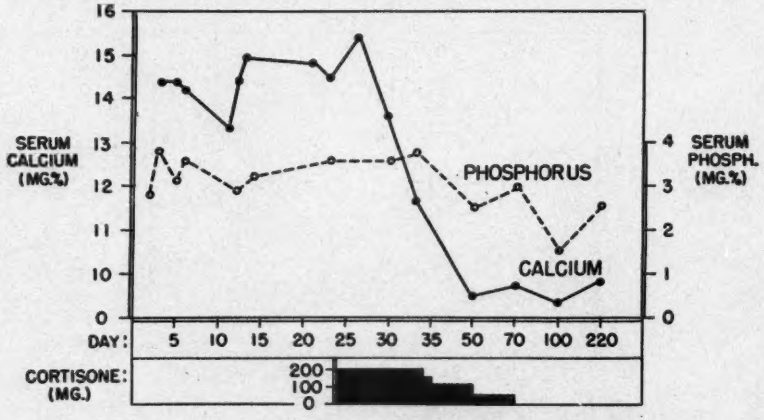

FIG. 2. *Case 2.* Calcium and phosphorus response to cortisone.

received a low calcium diet for three days, urinary calcium excretion rates were 136, 110 and 128 mg. per 24 hours on three successive days. Analysis of the stone removed from the right kidney one month prior to admission showed that 172 of the total 900 mg. were calcium. No further analysis of the stone was done.

Course in Hospital: The diagnosis of hyperparathyroidism was made initially because of hypercalcemia, low normal serum phosphorus levels, azotemia, and failure to obtain a history of vitamin D ingestion or evidence of multiple myeloma or metastatic carcinoma. Surgical exploration of the neck was performed on the twelfth hospital day and no parathyroid adenoma was found. On the nineteenth day a call to the local druggist revealed that the patient had been taking up to 300,000 units of vitamin D daily intermittently for three years without a prescription. The diagnosis was obvious at this point, and cortisone was started on the twenty-fourth day in a dosage of 200 mg. per day (figure 2). There was clearing of the mental status within 48 hours, and return of serum calcium to normal within eight days after cortisone was begun. Recovery was complete, and the patient manifested no further evidence of vitamin D intoxication in the 29-month follow-up period of study. At her last examination, on September 19, 1956, the serum nonprotein nitrogen was 42 mg. per 100 c.c. However, she has had persistent hypertension, in a range from 170/110 to 220/130 mm. of Hg.

Discussion

The two cases reported were elderly adults who were given large doses of vitamin D by their druggists without prescriptions from physicians. Neither could give a history of vitamin D ingestion, and each presented severe mental confusion, dehydration, and hypokalemic alkalosis. The cases illustrate the importance of prompt diagnosis and therapy of vitamin D intoxication, and afford an opportunity to review hypercalcemic states and their relationship to vitamin D and adrenal cortical steroids.

The clinical features of vitamin D intoxication have been well described in recent reviews,[3-6] and are summarized in table 3. Other diseases associated with hypercalcemia which must be differentiated from vitamin D intoxication include multiple myeloma,[7] metastatic carcinoma involving

Table 3

Clinical Features of Vitamin D Intoxication

System Involved	Manifestations of Vitamin D Intoxication
General	Weakness, fatigability, weight loss, excessive thirst
Gastrointestinal	Nausea, vomiting, cramps, constipation, dry mouth
Neuropsychiatric	Headache, paresthesias, vertigo, psychosis, depression, memory loss, coma
Hematological	Normocytic normochromic anemia
Urological	Polyuria, frequency, nocturia, fixed low specific gravity, renal insufficiency
Chemical	Hypercalcemia, normophosphatemia, azotemia, hypercalciuria, hypokalemic alkalosis, positive urine Sulkowitch reaction
Ophthalmological	Calcified scleral nodules, band keratitis
Pathologic	Calcification of heart, kidneys, lungs, blood vessels, stomach, thyroid, pancreas, and periarticular tissues

bone,[7] sarcoidosis, primary hyperparathyroidism, idiopathic hypercalcemia of infancy,[8] Hodgkin's disease,[9] leukemia,[10] Burnett's syndrome,[11] acute osteoporosis of disuse,[7] and primary carcinoma without bone destruction.[12] The diagnosis of hypervitaminosis D is established by the history of excess vitamin D ingestion, chemical findings of hypercalcemia, hypercalciuria and normophosphatemia, and by the response to therapy.

The physiologic effects of vitamin D are still not completely understood. Albright et al.[13] have shown that a major effect of vitamin D is to increase the intestinal absorption of calcium, and that there is a lesser parathyroid hormone-like effect to cause primary resorption of bone calcium and increased renal excretion of phosphate. Harrison[14] demonstrated in rachitic puppies that vitamin D administration caused increased tubular reabsorption and thereby decreased renal excretion of phosphate. Kodicek,[15] in a recent review, states that other effects of vitamin D administration include increased serum citrate levels and hypercitraturia, as well as a decreased serum phosphatase activity.

Much has been learned in recent years about the interrelationships of hypercalcemic states, vitamin D, and the adrenocortical steroids. There are now extensive data suggesting an antivitamin D action of the adrenal glucocorticoids. In 1936 Freyberg and Grant [16] demonstrated an elevated fecal calcium excretion in patients with Cushing's syndrome, and suggested that this was related to decreased intestinal absorption of calcium. This observation was confirmed by Soffer [17] but not by Albright.[18] Moehlig and Steinbach [18] observed in 1954 that patients with hypoparathyroidism who were well regulated on tachysterol developed tetany when given cortisone for arthritis. Colcher [19] in 1953 reported three patients with sprue who developed tetany while being treated with glucocorticoids for arthritis. The latter authors further noted that the tetany in these patients was refractory to the usual doses of vitamin D.

Further support for the concept of antagonism between the adrenal glucocorticoids and vitamin D has been derived from the study of patients with sarcoidosis. Harrell and Fisher [20] showed in 1939 that patients with this disease were unusually sensitive to vitamin D, and that hypercalcemia developed in some patients while receiving small doses of cod liver oil. In 1953 Dent [21] demonstrated that patients with sarcoidosis and hypercalcemia had increased intestinal absorption of calcium, and that cortisone therapy both decreased this intestinal absorption and lowered serum calcium levels to normal. More recently, Henneman et al.[13] have confirmed the findings of increased intestinal absorption of calcium in sarcoidosis with hypercalcemia, and they further found a hypercalcemia greater than could be accounted for by increased intestinal absorption alone. These observations suggested to the authors that the hypercalcemia of sarcoidosis is analogous to endogenous vitamin D intoxication. Our own experience has borne out the reduction of serum calcium levels by cortisone in sarcoidosis.

With the emergence of the concept of vitamin D antagonism by glucocorticoids, Anderson et al.[22] suggested treating hypervitaminosis D with cortisone. Prior to this time, treatment of vitamin D intoxication consisted simply of withdrawing the vitamin, forcing fluids and feeding a low calcium diet. In patients so treated in Howard's series,[6] the average time required for restoration of normal serum calcium levels was two to three months, and renal insufficiency persisted for as long as 18 months in some cases. More recently, Connor et al.[23] have reported dramatic lowering of serum calcium in patients with hypervitaminosis D treated with cortisone. Serum calcium was lowered to normal in one of their patients, even though intoxicating doses of vitamin D were continued during cortisone administration. This observation is amply confirmed by the excellent response to cortisone therapy obtained in both our patients, serum calcium levels returning to normal in eight and 13 days, respectively. In each case the response to cortisone was prompt, lasting and free of serious complications,

and we consider cortisone an important addition to the therapeutic regimen of the critically ill patient with hypervitaminosis D.

In addition to its therapeutic usefulness, cortisone may be given as a diagnostic trial in distinguishing the hypercalcemia of hyperparathyroidism from that of other etiologies. Cortisone therapy does not affect the hypercalcemia of hyperparathyroidism, whereas that of hypervitaminosis D and sarcoidosis is reduced greatly within 10 days after beginning cortisone administration in doses of 150 to 200 mg. per day.[24] We have confirmed the absence of an effect of cortisone on the hypercalcemia of hyperparathyroidism in a single case. Kabakow, Mines and King [9] recently reported a transient reduction of serum calcium levels during cortisone therapy in a patient with Hodgkin's disease. However, we have recently observed a lack of effect of cortisone in a patient with hypercalcemia due to metastatic bronchogenic carcinoma. Further experience is obviously needed in this area; however, all reports thus far have indicated a prompt reduction of the hypercalcemia of hypervitaminosis D.

Another point worthy of emphasis is the marked derangement of fluid and electrolyte balance noted in each of our patients. Both were severely dehydrated and had hypokalemic alkalosis. Polyuria, commonly associated with both hypercalcemia and hypokalemia, was prominent and contributed greatly to the dehydration in each patient. Continued vigil of fluid balance was mandatory for many days after initiation of therapy in these patients. Case 1 had a transient hypotensive episode on the eighteenth hospital day seemingly related to marked dehydration resulting from a negative water balance during several preceding days. The response to hydration was dramatic. Factors contributing to the potassium depletion were anorexia with deficient food intake and excessive losses of water and electrolytes due to vomiting and polyuria, all being characteristic clinical manifestations of the hypercalcemic state. No direct effect of vitamin D on potassium absorption and excretion could be found in the literature. The striking mental confusion in each of our patients was possibly related to the combination of hypercalcemia, dehydration and hypokalemic alkalosis. Replacement of fluids and electrolytes in case 2 led to some improvement in mental status prior to cortisone administration and at a time when serum calcium levels were at their highest. Large fluid intakes and potassium supplements were necessary throughout the course of therapy in these patients. Indeed, the marked clearing of the mental status 48 hours after the initiation of cortisone therapy was certainly in part related to continued restoration of fluid and electrolyte balance.

Finally, it is important to stress that the uremia of hypervitaminosis D is a reversible process,[25] and that untreated cases may progress to death in renal failure with metastatic calcification.[26] The prompt restitution of normal serum calcium levels by cortisone administration would favor a more rapid resolution of uremia in these patients.

Summary

1. Two cases of vitamin D intoxication are reported occurring in elderly adults presenting clinical syndromes of mental confusion, dehydration, polyuria and hypokalemic alkalosis.

2. Each had received intoxicating doses of vitamin D from druggists without a physician's prescription.

3. Cortisone therapy resulted in improved mental status in 48 hours, and return of serum calcium to normal in eight and 13 days, respectively.

4. The actions of vitamin D are reviewed and the interrelationships between hypercalcemic states, vitamin D and adrenal glucocorticoids summarized.

Summario in Interlingua

Es reportate duo casos de intoxication per vitamina D. Le patientes esseva adultos de etate avantiate qui se presentava con confusion mental, dishydratation, e alcalosis hypokalemic. Ambes habeva recipite grande doses de vitamina D per lor apothecario local sin recepta scribite per un medico, e ni le un ni le altere poteva rememorar se un previe historia de ingestion de vitamina. In ambes le studio hematochimic revelava hypercalcemia, normophosphatemia, hypokalemia, e azotemia. Tests de Sulkowitch esseva positive. Le collo de un del patientes esseva explorate chirurgicamente in consequentia del suspicion de hyperparathyroidismo ante que le historia del ingestion excessive de vitamina D esseva extrahite ab le apothecario local. Le un e le altere del patientes habeva ingerite inter 200.000 e 300.000 unitates de vitamina D per die durante plus que un mense ante le admission al hospital.

Ambe patientes esseva tractate con cortisona, proque illes esseva considerate como troppo malade pro un simple procedura de hydratation con therapia de dishabituation. Lor stato mental se meliorava dramaticamente intra 48 horas, e le valores del calcium seral esseva restaurate al norma in octo dies post le initiation del curso de cortisona in un del casos e in 13 dies in le altere. Le restablimento esseva complete in ambe patientes. Remaneva nulle effectos residue de hypervitaminosis D, ben que in ambe casos il esseva necessari prestar multe attention al balancia de fluido e de electrolytos durante le phase acute.

Es presentate un revista del mechanismos de action de vitamina D. Le problema del diagnose differential de hypercalcemia es discutite. Le relation inter statos hypercalcemic, vitamina D, e glucocorticoides adrenal es summaristate.

BIBLIOGRAPHY

1. Hess, A. F., and Lewis, J. M.: Clinical experience with irradiated ergosterol, J. A. M. A. 91: 783–788, 1928.
2. Donegan, C. K., Messer, A. L., and Orgain, E. S.: Vitamin D intoxication due to estron: report of two cases, Ann. Int. Med. 30: 429–435, 1949.
3. Anning, S. T., Dawson, J., Dolby, D. E., and Ingram, J. T.: Toxic effects of calciferol, Quart. J. Med. 17: 203–228, 1948.
4. Chaplin, H., Jr., Clark, L. D., and Ropes, M. W.: Vitamin D intoxication, Am. J. M. Sc. 221: 369–378, 1951.
5. Covey, G. W., and Whitlock, H. H.: Intoxication resulting from the administration of massive doses of vitamin D, with report of five cases, Ann. Int. Med. 25: 508–515, 1946.
6. Howard, J. E., and Meyer, R. J.: Intoxication with vitamin D, J. Clin. Endocrinol. 8: 895–910, 1948.

7. Albright, F.: The parathyroid glands and metabolic bone disease, 1948, The Williams and Wilkins Co., Baltimore.
8. Lightwood, R.: Idiopathic hypercalcemia with failure to thrive: nephrocalcinosis, Proc. Roy. Soc. Med. **45**: 401–402, 1952.
9. Kabakow, B., Mines, M. F., and King, F. H.: Hypercalcemia in Hodgkin's disease, New England J. Med. **256**: 59–62, 1956.
10. Mawdsley, C., and Holman, R. L.: Hypercalcemia in acute leukemia, Lancet **1**: 78, 1957.
11. Burnett, C. H., Commons, R. R., Albright, F., and Howard, J. E.: Hypercalcemia without hypercalciuria or hypophosphatemia, calcinosis, and renal insufficiency; syndrome following prolonged intake of milk and alkali, New England J. Med. **240**: 787–794, 1949.
12. Plimpton, C. H., and Gellhorn, A.: Hypercalcemia in malignant disease without evidence of bone destruction, Am. J. Med. **21**: 750–759, 1956.
13. Henneman, P. H., Dempsey, E. F., Carroll, E. L., and Albright, F.: The cause of hypercalcemia in sarcoid and its treatment with cortisone and sodium phytate, J. Clin. Investigation **35**: 1229–1242, 1956.
14. Harrison, H. E., and Harrison, H. C.: The renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone, J. Clin. Investigation **20**: 47–55, 1941.
15. Kodicek, E.: Metabolic studies on vitamin D, *in* Ciba Foundation Symposium, Bone structure and metabolism, 1956, Little, Brown and Company, Boston, pp. 161–174.
16. Freyberg, R. H., and Grant, R. L.: Calcium and phosphorus metabolism in a verified case of pituitary basophilism, Arch. Int. Med. **58**: 213–228, 1936.
17. Soffer, L. J.: Symposium on endocrine and metabolic disorder; ACTH and cortisone; physiologic and clinical considerations, M. Clin. North America **36**: 791–809, 1952.
18. Moehlig, R. C., and Steinbach, A. L.: Cortisone interference with calcium therapy in hypoparathyroidism, J. A. M. A. **154**: 42–44, 1954.
19. Colcher, H., Drachman, S. R., and Adlersberg, D.: Management of intractable sprue with cortisone and adrenocorticotropin (ACTH), Ann. Int. Med. **38**: 554–568, 1953.
20. Harrell, G. T., and Fisher, S.: Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium and phosphatase values, J. Clin. Investigation **18**: 687–693, 1939.
21. Dent, C. E., Flynn, F. V., and Nabarro, J. D. N.: Hypercalcemia and impairment of renal function in generalized sarcoidosis, Brit. M. J. **2**: 808–810, 1953.
22. Anderson, J., Harper, C., Dent, C. E., and Philpot, G. R.: Effect of cortisone on calcium metabolism in sarcoidosis with hypercalcemia, Lancet **2**: 720–724, 1954.
23. Connor, T. B., Hopkins, T. R., Thomas, W. C., Jr., Carey, R. A., and Howard, J. E.: The use of cortisone and ACTH in hypercalcemic states, Abstracts of papers presented at the thirty-eighth annual meeting of the Endocrine Society, J. Clin. Endocrinol. and Metabolism, Abstract 75, **16**: 945, 1956.
24. Dent, C. E.: Cortisone test for hyperparathyroidism, Letter to the editor, Brit. M. J. **1**: 230, 1956.
25. Adams, F. D.: Reversible uremia with hypercalcemia due to vitamin D intoxication, New England J. Med. **244**: 590–592, 1951.
26. Kaufman, P., Beck, R. D., and Wiseman, R. D.: Vitamin D therapy in arthritis: treatment followed by massive metastatic calcification, renal damage, and death, J. A. M. A. **134**: 688–690, 1947.

CONGENITAL CYSTIC DISEASE OF THE LUNG WITH PROGRESSIVE PULMONARY FIBROSIS AND CARCINOMATOSIS*

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THE subject of this communication is a condition which probably can most appropriately be termed *hereditary miliary broncho-alveolar cystic disease.* However, because of the cumbersome nature of this designation, the well established terminology *congenital cystic disease of the lung* has been retained.

The purposes of this communication are four: (1) to present evidence supporting the hereditary nature of the disorder; (2) to indicate that clubbed fingers on the basis of this disorder can exist for most of the patient's lifetime—for decades before any clinical evidences of pulmonary disease are detectable; (3) to demonstrate that the clinical picture may be that of idiopathic diffuse pulmonary fibrosis with the alveolocapillary block syndrome and/or cor pulmonale, and (4) to point out that bronchogenic carcinoma may occur as a fatal complication.

CASE REPORTS

Case 1. A white man was 32 years old at the time he was studied at The Johns Hopkins Hospital in 1949. He died at home on January 7, 1950. He had come to the hospital because of dyspnea and occasional orthopnea and palpitation for the preceding two or three years.

The father, who was said to have had arteriosclerosis and hypertension, had died at the age of 57 years of a cerebral hemorrhage. He is said to have had clubbed fingers. The mother (born in 1895) was living but had hypertension. A maternal aunt, an ovarian dwarf who had been a patient at The Johns Hopkins Hospital, survived almost six years after the first detection of metastases of a malignant melanoma, dying finally of generalized spread.[11] A paternal uncle was in a veterans hospital for many years prior to his death. The patient's generation consisted of three male sibs (including the patient) and one female. Besides the two males of this generation described here in detail, brother R. B. and sister B. have been studied and found to show no abnormality on physical examination or by x-ray of the chest.

The patient was born in Baltimore. He left school after the eighth grade and went to work as a carpenter. He worked for approximately 10 years, mainly on interior work. During this period there was exposure to silica sandpaper. The only other industrial exposure of apparent possible significance was that involved in a year's employment about 1938 in a textile mill where he carded wool. He was

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married and had a child, an albino, born in 1944. He was rejected for service in the Army.

The patient was under the impression that his fingers had been clubbed since at least age 18. He was, however, normal at birth and no cyanosis had been noted in early life.

About 1946 there was the insidious development of exertional dyspnea with palpitation and occasional nonradiating precordial pain which was related only to physical exertion and felt "as if a rib was broken." The patient had the impression that he had been somewhat dyspneic from childhood, or at least from about age 12. The dyspnea was steadily progressive until by the fall of 1948 he became dyspneic with any walking or with talking and found it necessary to use three pillows at night. He gave up work entirely. Digitalis appeared to be of some benefit, although at other times he suspected that it was responsible for his palpitations. He lost weight steadily (from 160 to 130 pounds). He noted ankle edema on only one brief occasion. In March, 1949, he had what was called "virus pneumonia," manifested by a dry, exhausting cough lasting about three days. The patient smoked very little.

Physical examination revealed a tall, thin, well developed but undernourished man. He was 70½ inches tall and weighed 127 pounds. There was slight cyanosis but no jaundice or edema. Respirations were rapid (28 a minute) at rest. There were rather marked kyphosis and scoliosis of the upper dorsal spine. There was no lymph node enlargement. Chest expansion appeared adequate. A few atelectatic râles were heard at the right base. The breath sounds were not remarkable.

The precordium was overactive and the rate totally irregular, so that auricular fibrillation was believed to be present. The ventricular rate was 60 per minute, however, and there was no pulse deficit. The heart was not enlarged and there was no precordial bulge or lift. The second pulmonic sound was greatly accentuated and split, with no other definite auscultatory abnormality. The blood pressure was 106/66 mm. Hg in both arms. There was mild gynecomastia on the right which was said to have been present for several weeks. There was no ascites, hepatomegaly or peripheral edema.

Laboratory findings included the following: white count, 13,950; hematocrit, 51.6%, with normal indices. X-rays of the chest (figure 1A) revealed diffuse pulmonary fibrosis bilaterally. The heart (including the left atrium) was not enlarged, but the pulmonary artery was very prominent. An electrocardiogram taken in March, 1949, was interpreted as showing marked sinus bradycardia with occasional sinus block and ventricular escape. All records showed marked right axis deviation and right ventricular hypertrophy and "strain." In June, 1949, the same pattern was present with a somewhat more rapid rate. After digitalis was discontinued, return to sinus rhythm occurred.

Studies of respiratory function by Dr. Ross L. McLean in July, 1949, revealed the following:

Tidal air	880 c.c.	an increase
Complemental air	1.47 L.	(2.17–3.62)*
Supplemental air	1.26 L.	(.63–1.33)
Vital capacity	2.52 L.	(2.8–4.95)
Minute volume	12.5 L./m²/min.	(3.1–4.5)
Maximal breathing capacity	92.2 L./min.	(82–169)
Breathing reserve	71 L.	(120)
Ratio of breathing reserve to M. B. C.	77%	
O_2 consumption/L. min. vol.	19.4	(36.3–53.8)
Arterial oxygen saturation	89%	(95%)
Arterial P_{CO_2}	21 mm. Hg	(about 40)
pH	7.5	(7.36–7.46)

Spirograms showed no evidence of obstruction.

* Normal range of values indicated in parentheses.

A B

FIG. 1. A. *Case 1.* June, 1949. There are diffuse reticulation of the lung fields and increased prominence of the pulmonary artery. B. Same, January 4, 1950 (three days before death). The heart is larger.

Cardiac catheterization by Dr. Richard J. Bing on July 26, 1949, revealed the following:

Cardiac output	3.71 L./min.	
Cardiac index	2.17 L.	(about 3.19 L./sq. meter b.s.a./min.)
Effective pulmonary flow	3.17 L., or 1.86 L./m².	(same as cardiac output)
Intrapulmonary shunt	14.3%	(virtually none)
PA pressure	70/34 mm. Hg	(30/15)
RV pressure	72/0 mm. Hg	(30/0)
RA pressure	6 mm. Hg	(10)

During the fall of 1949 the patient experienced several bouts of respiratory infection accompanied by marked increase in his dyspnea. A presystolic gallop was heard at times. When he was seen on January 4, 1950, the physical findings were essentially unchanged. There was no definite evidence of heart failure. X-ray of the chest (figure 1B) revealed considerable increase in the size of the heart. The patient died at home three days later.

Autopsy was not performed. The final clinical diagnosis was idiopathic pulmonary fibrosis with cor pulmonale.

Synopsis: A white male died of cor pulmonale at the age of 32 years. Clinically no basis was found for the pulmonary hypertension other than progressive, diffuse pulmonary fibrosis, causation obscure. Clubbing of the fingers had been present most of his life.

Case 2. A white man born in 1914 (brother of case 1) came to the hospital in the fall of 1951 at the age of 37 for investigation of his shortness of breath.

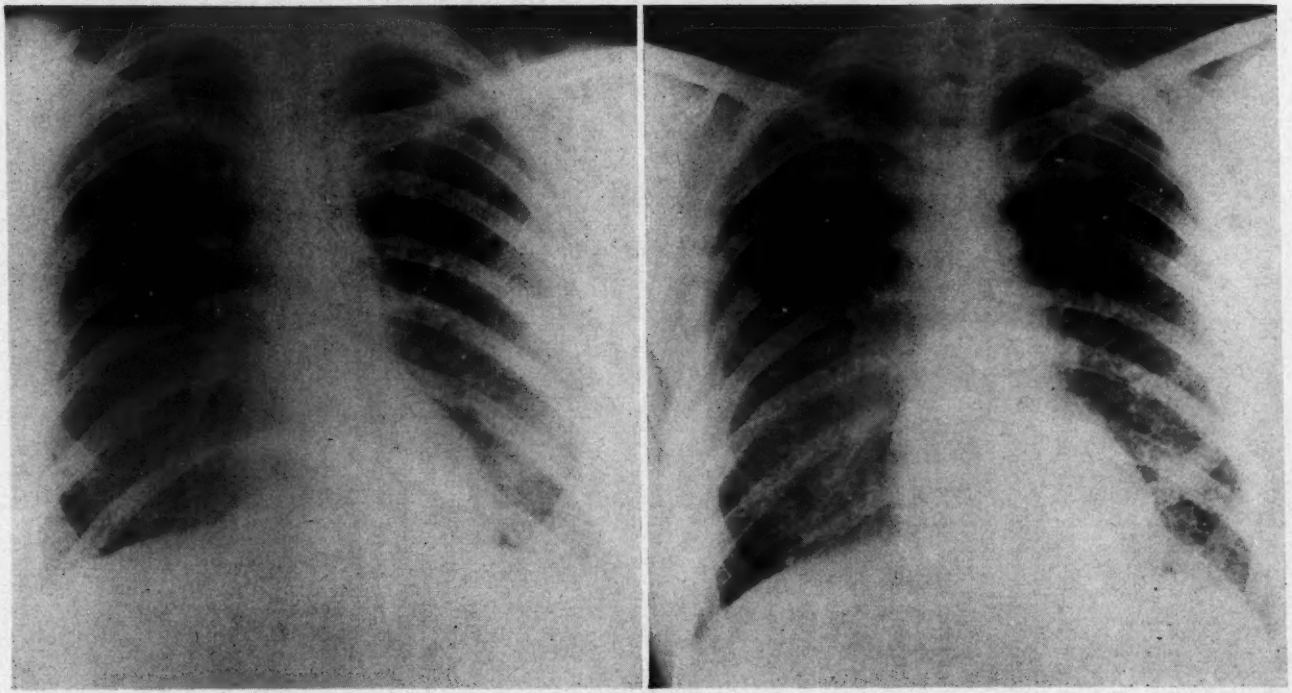
See case 1 for family history.

The patient had had scarlet fever at age 17 without recognized sequelae. At age 25 (1940) he had had "unequivocal" acute rheumatic fever with involvement of many joints, requiring five weeks of bed-rest and salicylates. Tonsillitis had occurred in 1949. All his life he had been unusually susceptible to colds and "croup." He dated the onset of his clubbed fingers at the age of 22 years (on another occasion, at 35 years). For about 14 years the patient had worked as a carpenter, with heavy exposures to sawdust and, to some extent, to silica sandpaper. For a short time in 1941 he had worked for a chemical company, where he was exposed to fumes. Furthermore, in his work as a maintenance man in a meat packing plant, he was required to go back and forth frequently between hot smoking-rooms and refrigerator rooms. He served in the Navy between 1942 and 1945. He had always been well during this period. In 1949 he had a bout of cellulitis on the right leg, secondary apparently to a patch of eczema related to varicose veins. Thereafter, he continued to have occasional pain and tenderness in this leg.

In January, 1950, he had had an attack of what he called "pleurisy" characterized by soreness of the left posterior thoracic area. Soon thereafter he noted the onset of a dry cough productive of very little white sputum. This cough continued to trouble him off and on. During 1951 he noted dyspnea, but this was mainly on exceptional exercise, such as running a mile or climbing three flights of stairs with a 50 pound tool box on his shoulder. He thought his clubbing had increased and that he tired more easily than usual.

Physical examination in October, 1951, revealed a well developed, well nourished man in no discomfort. He was 71½ inches tall and weighed 161½ pounds. The fingers and toes were clubbed but there was no cyanosis. The right tympanic membrane was perforated, and bone conduction was better than air conduction on that side.

The respiratory rate was normal. The thorax was symmetric, with slight increase in the A-P diameter. Breath sounds had a prolonged expiratory phase, and dry



A B

FIG. 2. A. *Case 2.* Fall, 1951. There is bilateral diffuse reticulation of the lung fields. B. Same, fall, 1953. The pulmonary changes are more striking, and consist of both reticulation and nodulation, with some increased radiolucency toward the apices, suggesting blebs or cysts.

inspiratory râles were heard throughout. The remainder of the examination, including that of the heart, was normal except for the right calf, which showed some increased heat, chronic pigmented dermatitis, and a circumference 1½ inches greater than that of the left calf. The blood pressure was 130/82 mm. Hg in both arms. There was no lymph node enlargement.

Laboratory studies revealed the following: hematocrit, 45%; white count, 6,600; vital capacity, 4.8 L.; maximal breathing capacity, normal (value not recorded); tuberculin, 1:1000, 2 plus. X-rays of the sinuses showed thickening of the lining membrane of both antra and poor definition of the ethmoid sinuses. X-ray of the chest revealed a diffuse reticular pattern of pulmonary fibrosis (figure 2A).

The patient was next seen in January, 1953. He had broken his nose in a fight in October, 1951, and had had much postnasal drip thereafter. He was now aware of considerable exertional dyspnea. He could not lie or sleep on his back because of a sensation of congestion in the upper chest. About twice a night he awoke with a sensation of gurgling of secretions in his lower airways. He would cough these out with relief.

Examination revealed a weight of 147 pounds. At the base of the right lung there were dry râles which persisted after coughing. Otherwise, the physical examination was unchanged.

Chest x-ray revealed no change in the heart and great vessels, which were of normal size and configuration, but the diffuse pulmonary fibrosis appeared to be more extensive than previously.

In April, 1953, the patient began to complain of severe pain in the tips of all the fingers and toes. This was worse at night, interfering seriously with sleep. Aspirin in large doses afforded little relief, but satisfactory relief was produced by codeine, 64 mg. at bedtime. X-rays of the hands and feet showed changes consistent with hypertrophic pulmonary osteoarthropathy.

Biopsy of the sternal marrow on May 6, 1953, revealed normal histologic sections and hematologic smears. There was specifically no evidence of Boeck's sarcoid. There was never any lymph node enlargement. The hematocrit was 44%.

Detailed studies of pulmonary diffusion and distribution were performed by Dr. Richard L. Riley on May 2 and May 20, 1953. In spite of cortisone therapy in the interval, the results were essentially the same and quite extraordinary. Ventilatory function was normal, yet diffusing capacity was very severely limited. The maximal breathing capacity was 179 L. per minute and vital capacity 4.35 L./min., whereas maximal diffusing capacity was 7 ml. O_2/mm. Hg gradient/sq. m.b.s.a. (an exceptionally low value when compared with the predicted normal of 33). There was elevation of the dead-space-to-tidal-volume ratio to 46%. Arterial blood was 79% saturated with oxygen when the patient was breathing room air, but with 25% oxygen became 94% saturated. P_{CO_2} and CO_2 combining power of whole arterial blood were reduced, presumably as a result of hyperpnea. These values were 31.1 mm. Hg and 18.3 mEq./L., respectively (normal, about 40 and 24). The findings differed from those in the cases of "alveolocapillary block" reported by Austrian et al.[1] by the presence of a normal vital capacity.

In May and June, 1953, the patient took 200 mg. of cortisone a day for 30 days, with only moderate subjective improvement in dyspnea and no objective improvement in respiratory function. There was clearing of the râles at the right lung base. He gained 18 pounds of weight and his blood pressure, which had been between 92/58 and 100/60, rose to a maximum of 140/90 mm. Hg. There was marked decrease in the amount of sputum he coughed up. There was genuine and marked relief of the pain in the fingers and toes. This returned, however, when cortisone was discontinued.

Beginning June 6, 1953, the patient received 1.5 gm. sulfadiazine a day in an attempt at prophylaxis against bronchial infection.

By August 24, 1953 the patient was considerably more dyspneic. (See x-ray of chest in figure 2B.) Even talking made him short of breath, yet he was able to continue full employment as a maintenance man for a meat packing firm. He had lost weight to 145 pounds. He noticed giddiness occasionally when exerting himself and almost always when assuming the upright position after stooping. The blood pressure was 98/58 mm. Hg, and the latter phenomenon may have been related to this. Giddiness during exertion was probably related to further lowering of arterial P_{CO_2} by hyperpnea.

During the following months the patient presented a picture which was even more pathetic. By October 13 he weighed only 130 pounds. Climbing stairs was almost completely out of the question. His sputum was fairly abundant and was purulent. Basilar râles were present, but in general the character of the breath sounds was not remarkable. P_2 was only slightly accentuated, and there were no clear signs of right ventricular hypertrophy.

On November 11, 1953, bronchograms were performed. These showed irregularities in the finer bronchial ramifications but nothing which could with certainty be labeled as bronchiectasis. No obstruction was demonstrated.

In spite of his progressive downward course, the patient continued to work until December 24, 1953. He was admitted to the Loch Raven Veterans Hospital on January 27, 1954. At this time he weighed only 125 pounds. The slightest exertion rendered him markedly dyspneic, with cyanosis of the nail-beds. However, at rest he was fairly comfortable. Examination of the chest revealed increased A-P diameter and active participation of accessory muscles in respiration. The lung fields were resonant to percussion. Over the right lung base posteriorly and laterally fine moist inspiratory râles were heard. The expiratory phase was normally rapid. The heart was not enlarged and there were no heaves or taps. The rhythm was regular but the rate was rapid (108 per minute). P_2 was greater than A_2. The blood pressure was 110/75 mm. Hg.

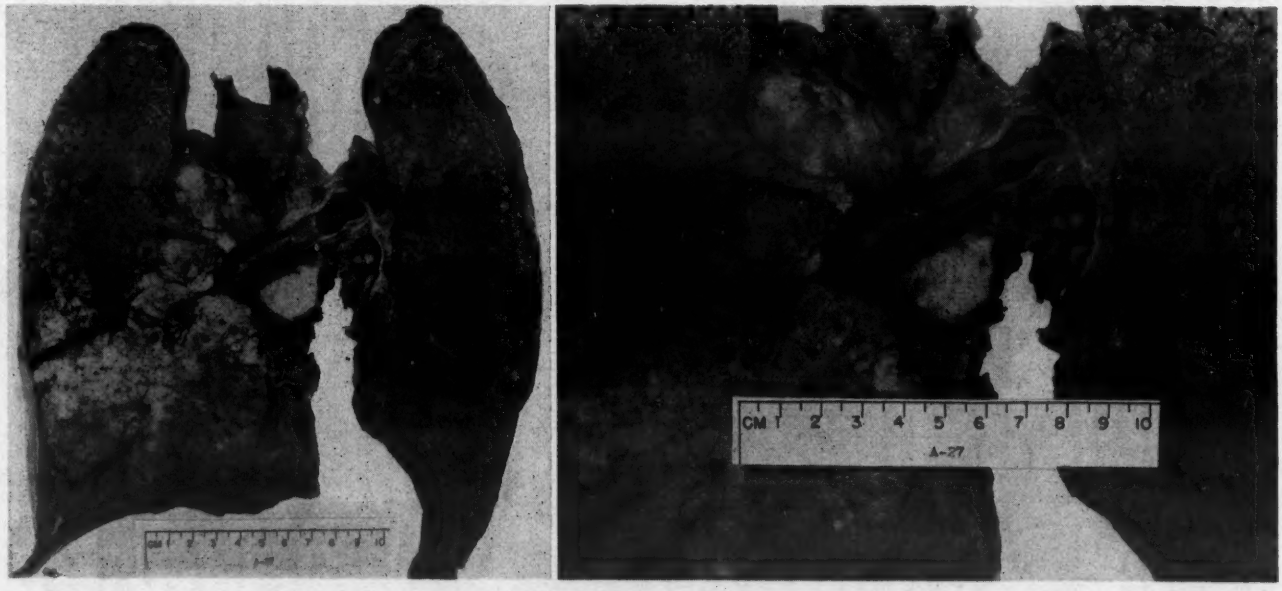
It is probably pertinent that iodized oil from the bronchograms performed two and one-half months previously was still present in large concentrations throughout both lung fields. There was a suspicion of a dense circular lesion measuring 5 cm. in diameter at the right lung base.

Further functional studies were performed. The vital capacity was now 4.2 L., and the maximal breathing capacity was 128 L. per minute. There was still no evidence of expiratory obstruction. Resting arterial oxygen saturation was 76%, with rise to 100% on breathing 100% oxygen.

On February 4, 1954, lung biopsy of the lingula was undertaken under general anesthesia. The left lung collapsed and expanded very poorly, and nodules 2 to 3 mm. in diameter were seen on its surface. Histologic study of the biopsy specimen revealed extensive proliferation of connective tissue, squamous metaplasia, and spaces lined with bronchial epithelium. As to the last, it was clear that this was an abnormal finding, since one would not normally expect to find bronchioles of that size in the tip of the lingula. The changes were considered consistent with Hamman-Rich's interstitial fibrosis.

Immediately after operation the patient was begun on cortisone, at first 300 mg. a day, tapering later to 200 mg. a day. After 10 days of this treatment the patient developed evidences of heart failure, necessitating more rigid salt restriction. Cortisone was continued for over a month, without perceptible improvement.

About February 28, 1954, the patient developed signs at the right lung base which were interpreted as those of fluid. Thoracentesis was productive of only 150 c.c., however. The changes progressed to involve the entire lower two thirds of the right lung field. The patient pursued a progressively downward course and died on March 12, 1954.



C D

FIG. 2. C. *Case 2,* autopsy specimen, showing "honeycomb lung" and extensive tumor. D. Same, closer view.

Autopsy was performed by Dr. Jack M. Burnett. The features of the gross examination were as follows: The body, weighing 51 Kg. and measuring 187 cm. in length, was very wasted, with marked digital clubbing. The other findings were limited to the thorax.

Both lungs (figure 2 C and D), stood up rigidly and completely filled both pleural cavities, even after they were opened, except for bloody hydrothorax on the right. There was a large mass of lymph nodes around the trachea and right lung hilum. A tumor 2 cm. in diameter completely occluded the bronchus to the right lower lobe. The lumina of the pulmonary veins were occupied by tumor in some instances. The left lower lobe was occupied by small gray nodules measuring up to 5 mm. in diameter. There was some subpleural spread.

Cystic areas were seen throughout both lungs but most pronounced in the right lower lobe, where they were interpreted as bronchiectatic and secondary to bronchial obstruction by the tumor.

Microscopic examinations revealed little normal lung. Fibrosis was very extensive. The cystic spaces were for the most part not lined with epithelium. Occasionally low cuboidal metaplasia was found. Two types of tumor cells were seen: (1) Large cells with sharp boundaries, eosinophilic cytoplasm, and irregular nuclei; these bore resemblances to stratified epithelium. (2) Highly undifferentiated, small and poorly demarcated cells in cords or clusters. Also, in several places alveoli lined by large irregular cells with somewhat bizarre nuclei were seen, and there was squamous metaplasia of bronchial epithelium.

One cannot be certain which was primary, the cysts or the fibrosis.

Synopsis: The brother of case 1 died at the age of 40 years after a progressively downhill course of several years' duration, manifested by radiologic evidence of diffuse and progressive pulmonary fibrosis, pain in the fingers and toes (which had been clubbed most of his life), and respiratory failure of the alveolocapillary block type. Autopsy revealed cysts of the lung, probably congenital, extensive fibrosis, and carcinomatosis of pulmonary origin.

Case 3. A 53 year old man was admitted to the hospital on April 14, 1955, and died approximately one month later from progressive respiratory failure. His complaint was shortness of breath from the age of about 15 years, with exacerbation in the last four months.

The father, a coal miner, had suffered from respiratory symptoms similar to the patient's, but these had been attributed to silicosis. He also had had clubbed fingers. Pneumonia was assigned as the immediate cause of the father's death at the age of 75 years. The mother was living and well at the age of 82 years. There were two sisters and one brother. One sister has clubbed fingers which were first pointed out to her by a physician in 1935. X-rays of the chest in this patient are negative, however. One sister, aged 56 years, had had tuberculosis which was now arrested. One son, age 21, was well and was a Navy flyer. One daughter, who also had hay fever and eczema, had died at a young age of epilepsy.

The patient had done office work for 30 years and had smoked 20 to 30 cigarettes a day for that entire period. In addition to the usual communicable childhood diseases, he had had diphtheria at age 11, scarlet fever at age nine, and pneumonia twice as a child. There were no known sequelae of these illnesses.

Ever since high school the patient had been aware of exertional dyspnea which limited his activity as compared with that of his compeers. This had persisted throughout his life but had become worse only in the last few months. By avoiding

undue exertion he was able to get along well. He had a cough which was occasionally productive of a little mucoid sputum. There was occasional wheezing. Clubbing of the fingers had been noted for his entire life. X-rays of the chest were taken periodically from 1926 on and had always been considered normal until March, 1952.

In December, 1954, the patient had had an illness diagnosed as pneumonia by his family physician. The patient felt that he had never recovered completely from this attack. His dyspnea was worse; there was more sputum which was often

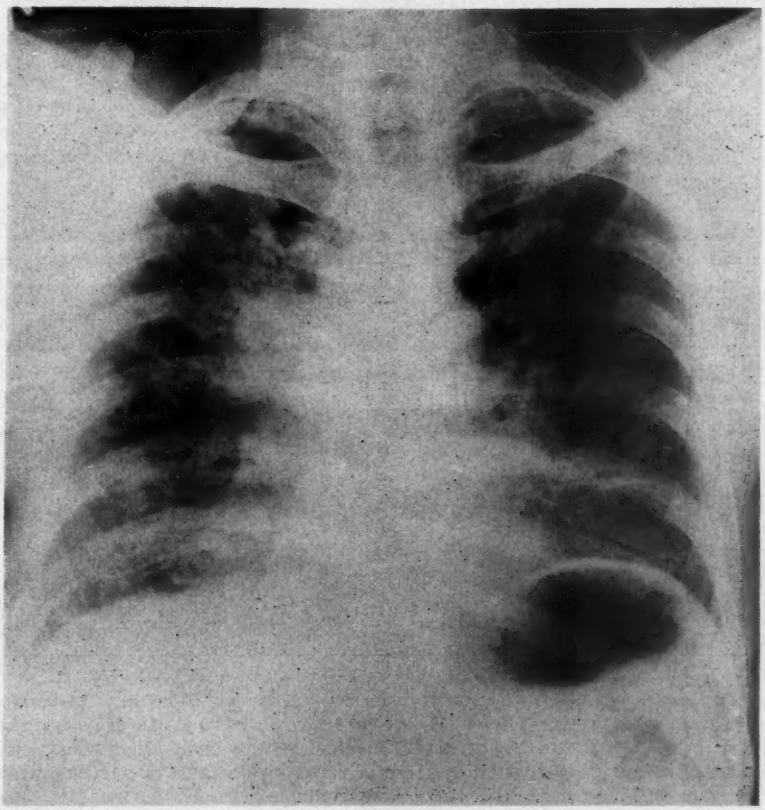


FIG. 3. A. *Case 3.* April, 1955. There are bilateral diffuse changes. At the right hilum there is a mass.

purulent, and he had an occasional sensation of tightness across the front of the chest. The wheezing was more pronounced. Climbing half a flight of stairs made him very short-winded. He lost about five pounds of weight.

Physical examination revealed a rather thin man who was dyspneic only with exertion. In general, he did not appear ill. There was an occasional dry cough. The chest expanded poorly but was definitely not emphysematous in configuration. Palpation and percussion were normal except that the lung bases descended poorly. At the right lung base posteriorly and anteriorly the breath sounds were broncho-

vesicular in character and associated with numerous fine râles which did not clear with coughing. The râles were particularly striking near the spine, where they extended up as far as the angle of the scapula. On the left the breath sounds at the base were again bronchovesicular, almost tubular, in quality, and were accompanied by showers of crepitant râles which likewise did not clear with coughing. No asthmatic wheezing was heard. The cardiovascular system was apparently normal. The blood pressure was 105/65 mm. Hg. The fingers and toes were rather markedly clubbed and the nail-beds slightly cyanotic. There was a small left inguinal hernia of the indirect type.

Review of x-rays revealed the following: In retrospect, a film in 1943 was seen to show mild fibrosis at the left base and definite elevation of the left leaf of the diaphragm. In 1948 this was more marked, there was some involvement at the right base, and both diaphragms were elevated, the left being higher than the right. By 1952 the fibrosis was more generalized. A film taken in February, 1955, showed enlargement of the mediastinal lymph nodes on the right. The changes interpreted as fibrotic in nature were extensive (figure 3A).

TABLE 1

Case 3	4/15/55	4/20/55	4/29/55	5/6/55	Normal
Vital capacity	1820 c.c. (47% normal)		1,663 (43%)	1,618 (42%)	
Maximal breathing capacity	95 l. (92% normal)		95 (91%)		
Diffusing capacity		7			40–60 ml. O_2/mm. Hg gradient
$\frac{\text{Dead space}}{\text{Tidal volume}} \times 100$		57			30%
Arterial blood					
O_2 saturation		84		87	94%
P_{O_2}		49		55	90 mm. Hg
P_{CO_2}		46		38	35–48 mm. Hg
CO_2 content		21.9		19.5	20–25 mEq./L.

Respiratory function studies were performed on four occasions in the laboratory of Dr. Richard L. Riley. The results are presented in table 1. In summary, these studies revealed fairly marked reduction in vital capacity, only slight reduction in maximum breathing capacity, no evidence of airway obstruction, a low oxygen diffusing capacity, high lung dead space, low arterial oxygen tension and saturation, and no significant alteration with hydrocortisone therapy.

Electrocardiogram was normal. There was no polycythemia. The white count ranged between 12,000 and 19,000 on four determinations; the patient was receiving hydrocortisone at the time of three of the determinations. Serum protein determinations revealed an albumin of 3.9 gm.% and a globulin of 4.7. Electrophoretic studies established an increase in alpha and beta globulins.

During his hospital stay the patient's pulse rate was always elevated out of proportion to his temperature. In spite of hydrocortisone, intermittent administration of oxygen, Achromycin and streptomycin and digitalization, the patient displayed progressively more respiratory distress and died on the thirtieth hospital day.

The only findings of note in the autopsy examination were those in the thorax. The lungs were very heavy, weighing together 1,650 gm. The lower portions of

FIG. 3. B. Autopsy specimen. Posterior view showing the tumor mass at the right hilum.

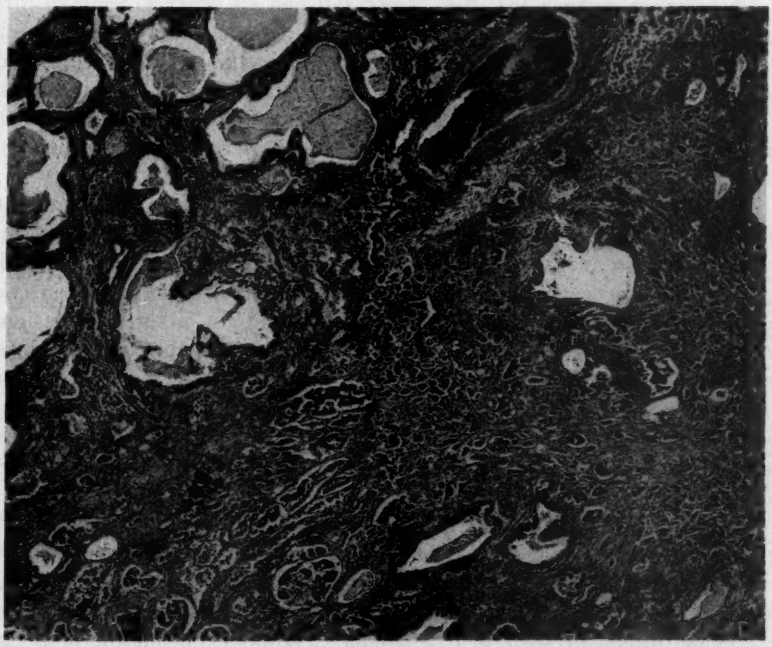


FIG. 3. C. Microscopic view from the right middle lobe. ×25. Cysts lined with cuboidal epithelium and numerous nests of carcinoma cells are demonstrated.

both lower lobes were the sites of numerous small cysts 1 to 2 mm. in diameter. In addition, small, firm, white, irregularly shaped nodules were distributed throughout both lungs. A large tumor mass had destroyed the wall of the bronchus of the right upper lobe and projected into it (figure 3B).

Histologically (figure 3C) the cysts were found to be lined with bronchial epithelium which in places was mucus-secreting. Smooth muscle strands were present in their walls, and much fibrosis was present throughout the lungs.

The tumor mass was squamous cell carcinoma. Tumor had seemingly been aspirated extensively throughout the lungs and was also distributed through the lymphatics. The absence of metastases elsewhere was surprising in view of the extensive involvement of both lungs.

Synopsis: A man with clubbing of his fingers all his life showed progressive pulmonary fibrosis over a period of 10 years. Weight loss and severe respiratory failure were striking features in the last months of life. Autopsy revealed numerous cysts of the lung, satisfying the usual criteria for congenital cysts, and bronchogenic carcinoma.

Discussion

Cystic Disease of the Lung: The type of cystic disease under discussion here—miliary cysts which are located particularly in the midportion of the lung and which satisfy criteria for congenital and hereditary origin (see below)—is probably rare. In 1937 Schenck [24] collected from the literature and his own experience 381 cases which satisfied his criteria; some of these were probably of the type under discussion. On the other hand, Caffey [6] writes as follows: "Anatomic studies indicate that this is an extremely rare condition; it has not been found at necropsy in the Babies Hospital (New York) during a period of 50 years." Undoubtedly, in some quarters the incidence has been exaggerated because of the failure to distinguish the cystic state which may accompany inflammatory involvement of the lung.

Tuberous sclerosis [8] and the Marfan syndrome [17] are two hereditary disorders in which cystic disease of the lung, indistinguishable from that which occurs as an isolated anomaly, occurs as an integral manifestation. An association of congenital lung cysts with anomalous pulmonary arteries in some cases is noteworthy.[15] "Honeycomb lung," a picturesque designation for a heterogeneous group, may also occur [12, 18] in the xanthomatoses, or histiocytoses (Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma). Cystic fibrosis of the pancreas is a heritable condition with certain pulmonary manifestations not likely to be confused with those in the three patients above. Survival to the age of even the youngest of our patients (case 1) is unheard of for cystic fibrosis of the pancreas.

The complications of true congenital cystic disease of the lung of the miliary broncho-alveolar type include progressive diffuse pulmonary fibrosis with alveolocapillary block [1] and/or cor pulmonale [5, 30, 32]; repeated pneumonias and other pulmonary infections, including occasionally chronic infection by organisms such as Friedländer's; repeated pneumothoraces; and carcinomatous degeneration.

The earliest radiologic sign—actually often the only sign until late in the patient's course—is generalized reticulation of the lung fields on ordinary radiogram of the chest. Bronchograms in the type of cystic disease under discussion are rarely positive. Laminagraphy may be helpful. Radiograms in full expiration should be compared with others in full inspiration.

Rarely is there cystic disease of other viscera.[19] As in congenital cystic disease of the kidney, cystic lung disease may be so severe as to kill in the neonatal period or early life,[10] or the victim may survive to adulthood, displaying, however, a progressive disorder with the complications enumerated above.

Heredity: The pieces of evidence for heritability of the cystic lung disease under discussion are three in number:

1. Familial aggregation might have another explanation, such as identical infection, nutrition, exposure to toxic or irritating materials, etc. However, since none of these seems likely in the cases at hand, the familial aggregation does argue for a genetic basis. In 1907 Sandoz [23] described identical twin sisters who died at the ages of 17 and 18 years of the same disease. The lungs demonstrated numerous cysts about 5 mm. in diameter, and the right side of the heart was greatly dilated. Actually, the reports of multiple cases in families are not numerous. MacRae [14] observed cysts, probably of a different type from that under discussion (large and limited in number), in four brothers from a sibship totaling 11 members.

2. The pathologic criteria, imperfectly satisfied in the first autopsied case (case 2)—columnar or cuboidal epithelial lining, smooth muscle and elastic fibers in the wall—tend to support a congenital origin. (These criteria may not be completely valid, since some pathologists believe cysts on the basis of emphysema, infection or pulmonary fibrosis can display these characteristics.)

3. An identical state, undoubtedly inherited, has been observed as an integral component of Marfan's syndrome.[17] Other manifestations of Marfan's syndrome, such as ectopia lentis, can occur as an isolated inherited anomaly, with a gene distinct from the "Marfan gene" responsible. Some cases of cystic disease of the lung seem to represent a comparable situation: a separate gene has produced a manifestation which, in other instances, can be an expression of the "Marfan gene."

Whether the trait under discussion is inherited as a recessive or dominant cannot, of course, be stated from this limited experience. The behavior, assuming that no parents and no children were involved, would suggest inheritance as a recessive.

Pulmonary Fibrosis: It is not relevant to discuss here the numerous causes of diffuse pulmonary fibrosis which have been identified, or the perplexing cases of idiopathic pulmonary fibrosis which are encountered with fair frequency. It is worthy of emphasis, however, that ***congenital cystic disease of the lung of the miliary type may present the clinical picture of idiopathic, progressive, diffuse pulmonary fibrosis.***

Probably repeated infection—possibly irritation by accumulated secretions—is responsible for the progressive fibrosis.

Multiple cases of idiopathic pulmonary fibrosis in families have been described in recent years: in identical twin sisters separated for 25 years before the onset of symptoms;[21, 22] mother, sister and daughter;[13] sisters,[13] and brothers.[29] The pathology has been thought to be that of Hamman-Rich's diffuse interstitial pulmonary fibrosis[9] in chronic form, but in certain of the cases congenital cystic disease has not been completely excluded.

Carcinomatous Degeneration: In 1941 Womack and Graham[31] found such pronounced epithelial metaplasia in three of nine specimens of congenital cystic disease of the lung that they speculated about the precancerous nature of this condition. Experience with cases 2 and 3 above has convinced us that carcinoma can be a complication of cystic disease of the lung. This may be a situation rather comparable to malignant degeneration in hereditary polyposis of the colon or in hereditary neurofibromatosis. Or more analogous may be the occurrence of malignancy in chronically infected and/or scarred areas, such as in the esophagus in achalasia,[16] in the skin in lupus vulgaris, in burn scars,[28] and in chronic varicose ulcers;[4] in the colon in chronic ulcerative colitis,[2] and in the lung in bronchiectasis[7] and perhaps chronic tuberculosis.[26]

Clubbing of the Fingers: The experience in the cases described does not assist in the understanding of this puzzling manifestation. It appears to be intimately related to the cystic disease of the lung. For many years, in all three patients, the clubbing could pass as isolated "simple" familial, presumably hereditary, clubbing, since there were absolutely no other clinical clues to the presence of cysts in the lung. Congenital cystic disease of the lung should at least be kept in mind—clinically it may be difficult to exclude —when instances of presumed familial clubbing are encountered.[8, 27, 33]

On rare occasion clubbing may precede other signs of bronchogenic carcinoma by several years.[25] The carcinoma of the lung and general progression of lung disease in cases 2 and 3 may have been responsible for the increase in clubbing, a feature accompanied by much pain in case 2.

Summary and Conclusions

There is a variety of congenital cystic disease of the lung which is genetically determined. The pulmonary lesions may be completely silent and resistant to clinical detection for many years. However, clubbing of the fingers and toes or more advanced forms of hypertrophic pulmonary osteoarthropathy may develop many years before subjective or objective pulmonary signs. The diffuse miliary variety of congenital cystic disease is likely to give rise to progressive, generalized pulmonary fibrosis with cor pulmonale and/or the syndrome of alveolocapillary block. Carcinomatous degeneration occurs as another late complication.

SUMMARIO IN INTERLINGUA

Super le base de tres casos in duo familias, un diffuse typo miliari de congenite morbo cystic del pulmon es describite. Es exprimite le opinion que le condition es determinate per genes. Digitos hippocratic pote disveloppar se a juvene etates, longemente ante le presentia de signos radiologic o altere. Le tableau clinic consiste typicamente de progressive fibrosis generalisate del pulmon con corde pulmonal e/o le syndrome de bloco alveolo-capillar. Carcinoma del pulmon occurre frequentemente in iste varietate de morbo cystic del pulmon. Iste complication esseva presente in duo del tres casos hic reportate.

BIBLIOGRAPHY

1. Austrian, R., McClement, J. H., Renzetti, A. D., Donald, K. W., Riley, R. L., and Cournand, A.: Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion, Am. J. Med. **11**: 667, 1951.
2. Bargen, J. A., Sauer, W. G., Sloan, W. P., and Gage, R. P.: Development of cancer in chronic ulcerative colitis, Gastroenterology **26**: 32, 1954.
3. Berg, G., and Zachrisson, C. G.: Cystic lung of rare origin—tuberous sclerosis, Acta radiol. **22**: 425, 1941.
4. Black, W.: Neoplastic disease occurring in varicose ulcers or eczema. Report of 6 cases, Brit. J. Cancer **6**: 120, 1952.
5. Bruce, T.: Über das klinische Bild verschiedener Typen von kongenitalen Zystenlungen bei Erwachsenen, Acta med. Scandinav. **102**: 295, 1939.
6. Caffey, J.: Pediatric x-ray diagnosis, 2nd Ed., 1950, Year Book Publishers, Chicago, p. 216.
7. Cureton, R. J. R., and Hill, I. M.: Malignant change in bronchiectasis, Thorax **10**: 131, 1955.
8. Davis, E.: Hereditary clubbing of digits in two families, Brit. M. J. **1**: 128, 1946.
9. Hamman, L., and Rich, A. R.: Acute diffuse interstitial fibrosis of the lungs, Bull. Johns Hopkins Hosp. **74**: 177, 1944.
10. Koontz, A. R.: Congenital cysts of the lung, Bull. Johns Hopkins Hosp. **37**: 340, 1925.
11. Levi, J. E., and Lewison, E. F.: Malignant melanoma in a patient with ovarian agenesis. Case report of prolonged survival, J. Clin. Endocrinol. and Metabolism **12**: 901, 1952.
12. MacDonald, A. M., and Shanks, R. A.: Honeycomb lung and xanthomatosis, Arch. Dis. Childhood **29**: 127, 1954.
13. MacMillan, J. M.: Familial pulmonary fibrosis, Dis. of Chest **20**: 426, 1951.
14. MacRae, D. F.: Congenital cystic disease of the lung. A familial incidence of four males in one family, Canad. M. A. J. **57**: 545, 1947.
15. Mannix, E. P., and Haight, C.: Anomalous pulmonary arteries and cystic disease of the lung, Medicine **34**: 193, 1955.
16. Mathews, E. C., and Vinson, P. P.: Carcinoma of esophagus complicating cardiospasm, Gastroenterology **15**: 747, 1950.
17. McKusick, V. A.: Heritable disorders of connective tissue, 1956, The C. V. Mosby Co., St. Louis, p. 65.
18. McLetchie, N. G., and Reynolds, D. P.: Histiocytic reticulosis and honeycomb lungs, Canad. M. A. J. **71**: 44, 1954.
19. Norris, R. F., and Tyson, R. M.: Pathogenesis of congenital polycystic lung and its correlation with polycystic disease of other epithelial organs; reconstruction of cystic elements in 2 cases, Am. J. Path. **23**: 1075, 1947.
20. Oechsli, W. R., and Miles, S. H.: Simultaneous bilateral spontaneous pneumothorax. A review of the literature and report of a recurrent case due to congenital cysts of the lung, Am. Rev. Tuberc. **30**: 239, 1934.

21. Peabody, J. W., Jr., Buechner, H. A., and Anderson, A. E.: Hamman-Rich syndrome: analysis of current concepts and report of three precipitous deaths following cortisone and corticotropin withdrawal, Arch. Int. Med. **92**: 806, 1953.
22. Peabody, J. W., Peabody, J. W., Jr., and Hayes, E. W.: Idiopathic pulmonary fibrosis: its occurrence in identical twin sisters, Dis. of Chest **18**: 330, 1950.
23. Sandoz, E.: Ueber zwei Fälle von Bronchiektasie, Beitr. z. path. Anat. u. z. allg. Path. **41**: 495, 1907.
24. Schenck, S. G.: Diagnosis of congenital cystic disease of the lung, Arch. Int. Med. **60**: 1, 1937.
25. Semple, T., and McCluskie, R. A.: Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma. A review based on 24 cases, Brit. M. J. **1**: 754, 1955.
26. Shafran, M. E., and Kavee, J.: The diagnosis of bronchogenic carcinoma in patients with pulmonary tuberculosis, Arch. Int. Med. **96**: 157, 1955.
27. Talbott, J. H., and Montgomery, W. R., Jr.: Familial clubbing of fingers and toes, Arch. Int. Med. **92**: 697, 1953.
28. Treves, N., and Pack, G. T.: The development of cancer in burn scars. An analysis and report of thirty-four cases, Surg., Gynec. and Obst. **51**: 749, 1930.
29. Wildberger, H. L., and Barclay, W. R.: Diffuse interstitial pulmonary fibrosis, Ann. Int. Med. **43**: 1127, 1955.
30. Willius, F. A.: Cardiac hypertrophy and failure secondary to diffuse, bilateral congenital cystic disease of the lungs, Proc. Staff Meet., Mayo Clin. **12**: 572, 1937.
31. Womack, N. A., and Graham, E. A.: Epithelial metaplasia in congenital cystic disease of the lung. Its possible relation to carcinoma of the bronchus, Am. J. Path. **17**: 645, 1941.
32. Wood, H. G.: Congenital cystic disease of the lungs: clinical study, J. A. M. A. **103**: 815, 1934.
33. Wurl, O. A.: Hereditary clubbing of fingers and toes; case report, Mil. Surgeon **105**: 217, 1949.

RESULTS OF SKIN TESTING IN MILITARY PERSONNEL *

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Introduction

In the last 10 years there has been much interest in the incidence of pulmonary calcifications in tuberculin-negative subjects with positive reactions to fungus antigens, particularly histoplasmin.[2, 3, 5] Skin testing surveys have been performed in many states, but studies in military groups have lagged until recently.[4] The importance of such investigations lies in the fact that pulmonary calcifications are used as criteria for induction purposes and for selection for various key positions, such as flying status. This study was also undertaken to ascertain the actual significance or validity of pulmonary calcifications in the presumptive x-ray diagnosis of healed primary tuberculosis. In addition, the potency of a commercial histoplasmin preparation (Lilly) was compared to an antigen prepared by one of us (J. S.).

Material and Methods

This survey was performed at Wurtsmith Air Force Base from January 19, 1953, to February 18, 1953. All personnel on the base during this period were tested with PPD No. 1,† PPD No. 2, histoplasmin, blastomycin and coccidioidin antigens. The two first fungus antigens were prepared by one of us (J. S.), the coccidioidin by Dr. C. E. Smith, and all were used in dilutions of 1:1,000. Commercial histoplasmin (Lilly), in a dilution of 1:1,000, was also administered. Separate syringes were kept for each of the antigens to eliminate the possibility of serologic cross-contamination.

Each subject received 0.1 c.c. of each of the above antigens intradermally on forearm sites, and these areas were read exactly 48 hours later. Indurated areas of 0.5 mm. or more were considered positive. Erythema alone was not interpreted as positive. Each participant was required to complete a detailed questionnaire, which provided such information as place of birth, place of longest successive residence, and various service locations.

Since blastomycin is prepared in an aqueous Merthiolate solution, individuals who reacted to blastomycin were further skin tested with a 1:1,000 Merthiolate solution in order to rule out Merthiolate sensitivity.

Teleroentgenograms, 14 x 17 cm., were taken of all positive reactors. X-rays were interpreted according to an arbitrary numerical grading system:

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† Purified protein derivative, first strength.

0—Normal x-ray; no evidence of calcification.
1—Hilar calcification less than 1 cm. in diameter.
2—Hilar calcification between 1 and 2 cm. in diameter.
3—Hilar calcification 2 cm. in diameter or greater.
4—Peripheral calcification less than 2 cm. in diameter.
5—Peripheral calcification greater than 2 cm. in diameter.
6—Multiple pulmonary calcifications of varying size.
7—Questionable reading, i.e., where it was difficult to decide between a calcification and a blood vessel on end.
8—Active infiltrative lesions.
9—Pleuritis, old.

Symbols L, R and B, indicating left, right and bilateral, respectively, were also used for more exact localization.

Results

A summary of all reactions is listed in table 1. Ten per cent of the group reacted to tuberculin, and 18% to histoplasmin. Most of the blastomycin reactors also showed positive reactions to histoplasmin. There were two isolated blastomycin reactors. One of these men had resided in Wisconsin, the other in upper New York State. There were six reactors to coccidioidin. All of these men had spent a long time in the coccidioidomycosis endemic areas.

Table 2 summarizes the correlation between pulmonary calcifications and the various positive reactors. The most significant finding is the much greater occurrence of pulmonary calcifications, both hilar and peripheral, in the histoplasmin-positive group as compared to the tuberculin-positive group. Thus only slightly greater than 50% of the tuberculin reactors exhibited pulmonary calcifications, whereas 80% of the histoplasmin reactors had pulmonary calcifications. Of some interest is the relative lack of calcification in the coccidioidin-positive group, although admittedly this is much too small a group on which to base such a trend.

Table 1

Distribution of Reactions to Antigens on Skin Test

Type	Number
None	527
Blastomycin	2
Blastomycin and other antigens	17
Coccidioidin	6
Histoplasmin	112
Histoplasmin and tuberculin	18
Tuberculin	77
Miscellaneous*	7
Total	766

* No x-rays on this group.

TABLE 2

Correlation Between Pulmonary Calcifications on X-Ray and Positive Reactions to Antigens

Type of Positive Reaction	Calcification		Type of Calcification	
	Present	Absent	Hilar	Multiple
Tuberculin	45	32	—	—
Histoplasmin	90	22	55	34
Tuberculin and histoplasmin	11	7	10	1
Blastomycin	0	2	—	—
Blastomycin and histoplasmin	12	4	7	5
Blastomycin and tuberculin	1	0	1	—
Coccidioidin	1	5	1	—

Table 3 is merely confirmatory of documented information in the epidemiology of the major fungus diseases. By far the greater number of histoplasmin reactors hailed from the histoplasmosis belt. All the coccidioidin reactors had spent varying periods of time in the endemic regions of this disease. One of the two blastomycin-positive subjects had lived in Wisconsin, an area considered endemic for this disease.

TABLE 3

Geographic Location and Positive Skin Test Reactions

Type	Total	Histoplasmosis Belt*	Other States
Histoplasmin	115	87	27
Histoplasmin and tuberculin	18	15	3
Blastomycin	2	0	2
Coccidioidin	6	0	6†
Histoplasmin and blastomycin	16	11	5

* Ohio, Kentucky, Tennessee, Indiana, Southern Illinois, Eastern Kansas, Missouri and southern Michigan.

† Coccidioidomycosis belt: California, New Mexico, Arizona and West Texas.

TABLE 4

Comparison Between Lilly and Schwarz Histoplasmin Antigens

	Number
Both positive	119
Both negative	629
Schwarz positive, Lilly negative	14
Schwarz negative, Lilly positive	13

Table 4 summarizes the comparison study between the Lilly histoplasmin antigen and the Schwarz antigen. Both antigens appear to be equal in validity and reliability.

DISCUSSION

Tuberculin sensitivity in this random group of young, healthy servicemen was approximately 10%, a figure in accord with the general trend of

tuberculin sensitivity throughout the country. Of considerable interest is the fact that a greater percentage of subjects reacted to histoplasmin. Thus, as emphasized by others, residence in the midwestern section of the country is more likely to result in exposure and sensitization to histoplasmosis than to tuberculosis. Furthermore, pulmonary calcifications were much more common in histoplasmin than in tuberculin reactors.[1, 6]

In the group of subjects with pulmonary calcifications associated with histoplasmin positivity, hilar calcifications were slightly more common than were parenchymal lesions. This phenomenon is being stressed in other current correlative surveys. In addition, we have found instances of larger hilar calcifications (between 1 and 2 cm. in diameter) in histoplasmin reactors. These findings suggest that evaluation of hilar calcifications should also include histoplasmin skin testing, especially when such calcifications exceed 1 cm. in diameter. The benign nature of such lesions should also be stressed, inasmuch as this study was a random sampling of healthy men.

The usual incidence of cross sensitization between histoplasmin and blastomycin was also encountered in this series. This of course emphasizes the need for careful evaluation of a blastomycin skin reaction.

Coccidioidin reactors all gave histories of ample exposure to the fungus. Actually, we were mildly surprised by the low number of reactors in this military group, the majority of whom had spent varying periods of time in the coccidioidomycosis endemic area. Thus, either coccidioidomycosis tends to affect fewer individuals subclinically than histoplasmosis, or skin sensitivity to coccidioidin tends to regress more rapidly. Since many people exposed to coccidioidomycosis handle the infection without serious sequelae, the latter possibility seems more probable. Calcareous deposits were uncommon in this series of coccidioidin reactors.[7, 8]

The commercial preparation of histoplasmin (Lilly) evaluated in this study displayed the same degree of potency and validity as the antigen prepared by us. It may be employed, therefore, with confidence in routine skin surveys for possible underlying fungus disease.

Summary

1. In a heterogeneous military group, 10% reacted to tuberculin and 18% to histoplasmin.

2. Pulmonary calcifications were observed with greater frequency in the histoplasmin-positive group. Many of these calcifications were located in the hilar regions, and considerable numbers of these were 1 cm. or larger in size.

3. Evaluation of parenchymal and hilar calcifications should always include histoplasmin skin testing.

4. Cross sensitization between histoplasmin and blastomycin was demonstrated in this series.

5. Apparently, exposure to coccidioidomycosis results in only a small proportion of skin sensitivity in those so exposed.

6. The Lilly brand of histoplasmin is valid and potent and may be used for routine testing.

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SUMMARIO IN INTERLINGUA

Iste studio de testation cutanee esseva executate in un gruppo heterogenee de juvene militares al Base Wurtsmith del Fortia Aeree inter le 19 de januario 1953 e le 18 de februario 1953. Un total de 766 homines esseva testate. Omne participante respondeva a un questionario que demandava informationes in re le loco de nascentia, le plus prolongate residentia continue, e previe stationes militar. Iste datos esseva utilisate subsequentemente in le analyse del resultatos.

Le personal total presente al base durante le periodo mentionate esseva testate con le sequente antigenos: purificate derivato de proteina del prime fortia, purificate derivato de proteina del secunde fortia, histoplasmina, blastomycina, e coccidioidina. Etiam un preparato commercial de histoplasmina (Lilly) esseva evalutate in iste studio. Teleroentgenogrammas de 14 per 17 cm esseva obtenite ab omne reactores positive. Illos esseva interpretate con referentias special al dimension e al sito (hilar o peripheric) de calcificationes pulmonar.

Reactiones positive a tuberculina esseva notate in 10% del gruppo, a histoplasmina in 18%. Duo individuos reageva positivemente a blastomycina e sex a coccidioidina. Non multo plus que 50% del reactores positive a tuberculina exhibiva calcificationes pulmonar. Inter le reactores positive a histoplasmina, calcificationes pulmonar esseva presente in 80% del casos. In iste ultime gruppo, calcificationes hilar esseva levemente plus frequente que calcificationes parenchymal. Le calcificationes hilar in le gruppo de reactores positive a histoplasmina includeva plures con diametros de inter 1 e 2 cm. Nulle del individuos con reactiones positive a coccidioidina exhibiva calcificationes pulmonar.

Iste resultatos confirma le conclusiones de simile studios per altere autores, a saper que residentia in le section del west central del Statos Unite resulta con plus alte grados de probabilitate in sensibilisation a histoplasmosis que in sensibilisation a tuberculosis. Le plus alte incidentia de calcificationes hilar—specialmente tales con grande diametros de inter 1 e 2 cm—in subjectos qui reage positivemente a histoplasmina suggere que le evalutation de tal calcificationes deberea includer tests cutanee a histoplasmina. Le paucitate de reactiones positive a coccidioidina in un grande gruppo de individuos amplemente exponite in areas de coccidioidomycosis endemic justifica le postulation que sensibilisation cutanee a coccidioidina regrede plus rapidemente que le sensibilisation cutanee al altere antigenos fungal. Le usual sensibilisation cruciate inter histoplasmina e blastomycina non esseva absente in le presente serie. Le preparato commercial de histoplasmina (Lilly) que esseva evalutate in iste studio monstrava le mesme grado de potentia e de validitate como le antigeno preparate per nos.

BIBLIOGRAPHY

1. Manos, N. E., Ferebee, S., and Kerschbaum, W. F.: Geographic variation in the prevalence of histoplasmin sensitivity, Dis. of Chest **29**: 649–668, 1956.

2. Palmer, C. E.: Nontuberculous pulmonary calcification and sensitivity to histoplasmin, Pub. Health Rep. **60**: 513–520, 1945.
3. Christie, A., and Petersen, J. C.: Pulmonary calcification in negative reactors to tuberculin, Am. J. Pub. Health **35**: 1131–1147, 1945.
4. Air University, U. S. Air Force School of Aviation Medicine: Studies on coccidioidomycosis at air force bases in the southwestern United States; numbered report, Randolph Field, Texas, December, 1954, p. 25.
5. Furcolow, M. L., High, R. H., and Allan, M. F.: Some epidemiological aspects of sensitivity to histoplasmin and tuberculin, Pub. Health Rep. **61**: 1132–1144, 1946.
6. Furcolow, M. L., and Sitterley, J.: Further studies of the geography of histoplasmin sensitivity in Kansas and Missouri, J. Kansas M. Soc. **52**: 584–589, 1951.
7. Schwarz, J., and Muth, J.: Coccidioidomycosis: a review, Am. J. M. Sc. **221**: 89–107, 1951.
8. Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. G., Beard, R. R., and Saito, M. T.: The use of coccidioidin, Am. Rev. Tuberc. **57**: 330–360, 1948.

ASYMPTOMATIC GASTRIC RETENTION IN DIABETICS (GASTROPARESIS DIABETICORUM) *

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THE incidental discovery of unsuspected and asymptomatic gastric retention in moderately severe diabetics led to a study of this condition. References to gastric retention in diabetes are very scanty in current literature.

Motility disturbances of the gastrointestinal tract in general have always been a part of the symptomatology of diabetes mellitus. Constipation and diarrhea, with or without anorexia and nausea, have been well known to accompany diabetes. "Diabetic diarrhea," nocturnal as well as diurnal, remains a severe complication. Marble [1] was one of the first to suggest the possibility of a neurogenic origin for this syndrome.

Gastric retention, in clinical medicine is most commonly due to pyloric obstruction resulting from peptic ulcer. Wood [2] clarified the fact that the clinical course of peptic ulcer, including its sequelae, is the same in diabetics as in those who never had or never developed diabetes. He noted the probability that in young diabetics the symptoms of peptic ulcer may be less typical, and therefore there may be more delay in diagnosing pyloric obstruction.

In 1951 Quigley [3] criticized the clinical concept of pylorospasm as a common cause of delayed gastric emptying. He and his group observed in animals that emotions, pain or reflexes from somatic or visceral sources commonly result in inhibitions of the pyloric sphincter as well as other portions of the digestive tract. According to these observers, under these conditions the delayed evacuation is due to a decrease in antral propulsive peristalsis and occurs commonly despite a patulous pylorus.

Rundles, in his excellent monograph on *Diabetic Neuropathy*,[4] emphasized the fact that disturbed gastrointestinal function is a common accompaniment of diabetic neuropathy, and suggested that, in view of the other evidence of disturbed autonomic nerve function, such as genitourinary disturbances, sphincter abnormalities and faulty sweating patterns, the gastrointestinal disturbances (including gastric retention in diabetics) should be considered as resulting from autonomic nerve disease.

Rundles, in collaboration with Hodges and Hanelin,[5] further investigated the dysfunctions of the intestinal tract accompanying neurologic diseases and selected 75 cases, of whom 35 had diabetic neuropathy, 20 had pernicious

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anemia, five tabes dorsalis, etc. Of their 35 selected diabetics, five showed findings similar to ours as far as delayed emptying of the stomach was concerned. Those diabetics and the other cases with neurologic disease revealed gastrointestinal abnormalities of a wide range, covered under the heading of "disordered motor function." The disordered motor function was manifested mainly by some degree of gastric retention and prolonged transit through the intestinal tract.

Golden and others described similar findings even earlier,[6] and suggested that the grossly disturbed function and roentgen appearance of the intestine may be due to degeneration of the nerves supplying the gut. Rundles and co-workers [5] noted that in many of their patients with diabetic neuropathy the deviation from normal, as far as gastrointestinal motor function is concerned, was greater among those with severe neuropathy. They also noted that the x-ray findings were of little value as to the nature of the clinical symptoms presented—"the same kind of abnormalities occurring in those with diarrhea, as well as with constipation,"—and found also that in cases of virtual absence of improvement in gastrointestinal symptoms the x-ray findings showed that return to normal had been incomplete.

In 1953 Martin [7] reported on diabetic neuropathy in diabetics with diarrhea, stating that of 14 cases with diabetic diarrhea examined, nine showed delay of gastric emptying.

Golden [8] stated that "an abnormal gastric residue cannot be taken as evidence of any particular disease, but it does mean that at least a physiologic disorder is present." All observations concerned with the emptying of the stomach after vagotomy [9] emphasized that there is no change in shape or size of the stomach, except that the expulsion of contents becomes very slow —complete emptying of the barium in 12 to 24 hours, as compared with the average normal time of two to two and one-half hours.

Our first case, having been embarrassingly accidental, was followed by study of 26 other routinely admitted diabetics.

Case Reports

Case 1. A 36 year old unemployed white farm laborer had had migratory polyarthritis at the age of 10 and again at the age of 17. He served in the Armed Forces from February 6, 1942, to July 8, 1943, had one other episode of polyarthritis, and was finally discharged with the diagnosis of valvular heart disease and rheumatic fever. There was no further recurrence of polyarthritis. In 1949 his diabetes was discovered, the usual symptoms presenting, and it was regulated with diet and insulin. He has had multiple hospitalizations in Veterans Administration and community hospitals. During one of the hospitalizations in another Veterans Administration hospital (WRJ) in 1952, after extensive studies the following diagnoses were made: diabetes mellitus, rheumatoid arthritis, malnutrition and avitaminosis. On his first hospitalization at this hospital (March 11 to May 20, 1954), his diabetes was controlled with little difficulty on a 2,600 calorie diabetic diet (300 gm. CHO, 115 gm. P, 100 gm. F), with 55 units of NPH insulin daily. The following diagnoses were established during that hospitalization: (1) diabetes mellitus; (2) peripheral neuritis,

diabetic; (3) malnutrition and avitaminosis, secondary to the above; (4) rheumatoid arthritis, multiple, minimal; (5) iridocyclitis, right, acute; (6) ulcerative colitis by history only (established on a previous hospitalization in another Veterans Administration hospital, but not found on x-ray or instrumental examination at this time).

In addition, a diffusely enlarged thyroid gland was found. At no time did this man have any complaints concerning his gastrointestinal tract, though he had had episodes of diarrhea in the past. He appeared to be a slow-spoken, somewhat dull, retiring individual. Because of the thyroid findings he was transferred to a large Veterans Administration hospital for thyroid studies, which established his case as euthyroid. While being studied he had an episode of from three to eight watery stools daily, and x-ray studies of the small intestine were attempted. On this occasion an enormously dilated stomach retaining barium meal and food was found. Repeat x-ray studies of the small bowel were attempted, but again were unsuccessful because of the gastric retention, and the patient was retransferred to our hospital. In our hospital the gastrointestinal series was repeated (June 15, 1954), and the findings were exactly the same as at the other Veterans Administration hospital 10 and 20 days previously (figure 1). Two weeks later (June 29, 1954) the x-ray studies of the stomach were repeated and revealed unchanged findings. The patient still refused to admit to any kind of gastric complaints but anorexia at this time. Succussion splash was heard over the enlarged stomach area, and the contour of the dilated stomach could be visualized through the abdominal wall and the dilated organ could be palpated. On July 26, 1954, four weeks after the previous x-ray studies and after repeated gastric lavages, and continuous and interrupted nasogastric suction, another x-ray study was done (figure 1). The patient became anorexic and "brittle" as a diabetic, with multiple hypoglycemic attacks and loss of weight. The x-ray studies, however, revealed practically no change from the previous findings. The patient's weight dropped to 105 pounds (his normal weight being supposedly 116), and his appearance changed from that of malnutrition almost to that of cachexia.

The laboratory data can only be summarized here. All serologic tests were negative. Repeated hemograms were normal, with hemoglobins ranging from 13.5 to 15 gm. Urines were essentially normal, except for glycosuria. Innumerable blood sugar determinations, aside from occasional fasting blood sugars of 350 mg.%, averaged satisfactory levels of about 120 mg.%. Multiple stool examinations ranged from negative to occasional 2 plus guaiac; they were always negative for ova and parasites, and negative for fat and striated muscle fibers. Serum electrolytes on many occasions revealed normal potassium, sodium, chloride and CO_2 values. Blood urea nitrogen was normal. Multiple gastric aspirations at first revealed persistent achlorhydria, with and without histamine, but later showed free hydrochloric acid to be present though of low level.

The eosinophil count showed 121; four hours after 25 mg. of ACTH it was 33. Barium enema was normal compared with the films taken three years ago in another Veterans Administration hospital, which at that time showed changes consistent with ulcerative colitis. Repeated gastroscopic examinations (Dr. Deutsch) revealed "chronic superficial gastritis"; one gastroscopy done after 48 hours of continuous suction revealed identical findings. Gastroscopic biopsy material revealed normal gastric mucosa. Peripheral muscle biopsies were considered "within normal," without evidence of collagen disease. Sigmoidoscopy on one occasion showed edematous ampulla, with an area of old pitted scars consistent with ulcerative colitis in an interim phase; biopsy of these areas showed "nonspecific chronic inflammation." At this time (August, 1954) the patient was sent home on leave for approximately four weeks; he was feeling well, his diabetes was under control, and he had no diarrhea or no upper gastrointestinal complaints whatsoever. He was comfortable at home and had no diarrhea or any other complaints; however, his gastric x-ray on his return

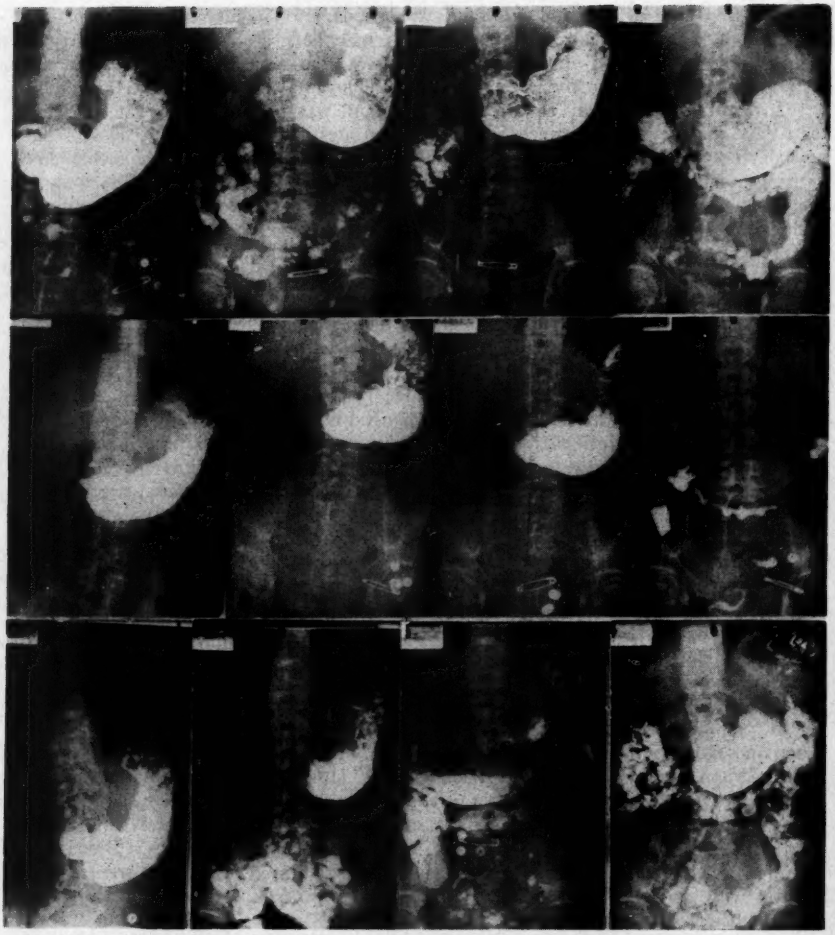

FIG. 1. *Case 1.* X-rays showing, in succession from left to right, the immediate, the three hour, the six hour and the 24 hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. *Upper,* June 15, 1954; *middle,* July 26, 1954; *lower,* February 5, 1957.

showed exactly the same findings as before. The gastric retention now was considered to be a sort of "vagotomy," which appeared to be explainable as a diabetic neuropathy involving the vagus nerve. The nutritional status of the patient and his inability to cope with it led to consideration of some type of surgical approach. The decision reached was after consultation with a large research hospital where his case was restudied (from September 10 to October 22, 1954). These studies again showed the gastric retention to be unchanged. The considered opinion of that hospital was in agreement with ours, that the gastric retention was an expression of autonomic dysfunction accompanying diabetes. Since the patient had no symptoms from his

gastric retention, and his gastric retention was considered to be due to the lack of propulsion rather than to obstruction, surgery was ruled out. A trial with Urecholine sublingually was made, with some potentiation of motor activity of the stomach. His diabetes was well controlled and his nutritional status appeared to improve. A 3,000-calorie diet, with 40 units of NPH insulin supplemented occasionally by five to 10 units of regular insulin daily, and gastric suction nightly for several weeks, appeared to be beneficial. During all of his hospitalizations he was given multiple vitamin supplements by mouth and injection. There were again no complaints as far as his stomach was concerned. On September 8, 1954, seven weeks after his last gastrointestinal series, another x-ray review was done which showed the gastric retention to be as before. The patient was feeling well and had gained three pounds, and was discharged to his home on December 30, 1954. To his diagnoses as enumerated above was added diabetic neuropathy, including vagus nerve secondary to diabetes, with asymptomatic gastric atony (gastroparesis diabeticorum).

His course at home was uneventful until September 29, 1956, when he was readmitted because of multiple abscesses and cellulitis in the nucheal area due to *Staphylococcus aureus*. Topical and systemic specific antibiotic treatment had to be alternated with surgical incision and drainage on multiple occasions until this infection was controlled. His diabetes was no problem during this admission. Multiple and severe nocturnal diarrheas were present. The patient refused intubations, remembering his past experiences with all types of tubing. He was given crystalline insulin four weeks prior to an x-ray study (figure 1) on February 5, 1957, which showed no change whatever concerning the gastric retention. He is being maintained on 30 units crystalline insulin and an 1,800-calorie diet at present. He maintains his weight at about 105 pounds, has no complaints, remains anorexic, and still has occasional mild bouts of diarrhea.

Case 2. A 36 year old white mechanic, a diabetic, four weeks before admission, had noticed an apparently spontaneous swelling of the left knee, and was hospitalized at a small community hospital where a diagnosis of abscess of the knee was made. He was treated with, among other things, local heat in the form of a heating pad, which caused a burn behind the left knee. Then surgical drainage of the left knee was performed, and the patient was discharged from that hospital following removal of the drains from the "abscess."

At the time of his admission to our hospital (on January 28, 1955), the burns were found and the patient's diabetes was poorly controlled, apparently because of secondary infection. He had had diabetes for 10 years usually in reasonable control by the use of 40 units of protamine zinc insulin daily, with 10 or occasionally 20 units of regular insulin in addition. He was admitted to the Surgical Service because of the burns, but soon was transferred to the Medical Service because of rather frequent hypoglycemic attacks, alternating with glycosuria. He was given a 2,200-calorie diabetic diet (220 gm. CHO, 90 gm. P and 100 gm. F), and 40 units of protamine zinc insulin, to which five regular insulin units were added. The infected skin areas showed prompt healing under topical treatment. Blood sugar ranged from 330 to 380 mg.% to normal to 38 mg.%, with severe hypoglycemic attacks in spite of all the usual trials of regulation with rigid control of food and activities.

The patient was a fairly well developed, thin, asthenic young white male of sallow complexion, looking chronically ill. Blood pressure was 100/80 mm. of Hg. The dorsalis pedis pulsations were reduced bilaterally as compared to the posterior tibials, which were of fair quality bilaterally. Vibration sense appeared reduced on some occasions and normal on others. The deep tendon reflexes were found to be hypoactive but equal bilaterally. There were occasional episodes of vague epigastric distress, which sometimes were associated with crampless diarrhea up to four times a day. Stool examinations were negative for parasites and blood. However, the

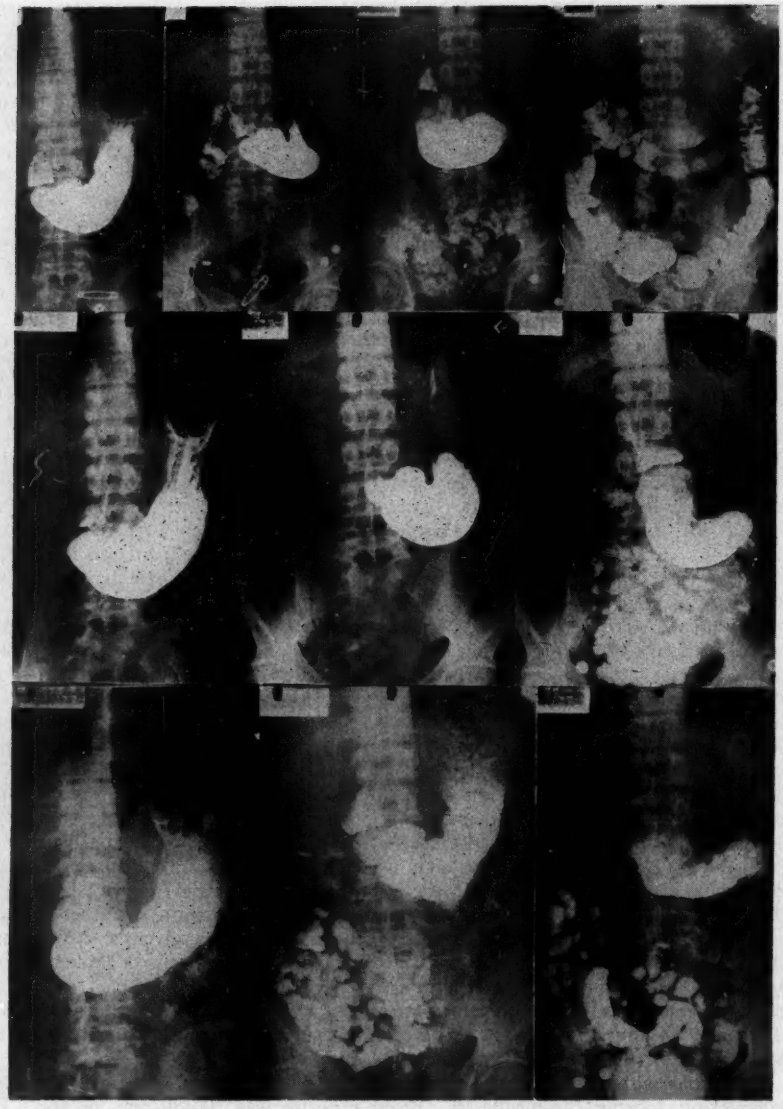

FIG. 2. *Case 2.* X-rays showing, in succession from left to right, the immediate, the three hour, the six hour and, if available, the 24 hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. *Upper,* March 7, 1955; *middle,* March 14, 1955; *lower,* April 25, 1955.

gastrointestinal series on March 7, 1955 (figure 2), revealed a hypotonic stomach and very sluggish peristalsis without any organic lesion. Pylorus, duodenal cap, loop and small bowel loops showed no abnormalities. At three hours there was still about 50% retention of the meal in the stomach. At six hours there was partial retention of the meal, but the head of the meal had reached the hepatic flexure. The small bowel showed no abnormality. Reëxamination on March 14, 1955, after suctioning, revealed a still markedly hypotonic stomach (figure 2) with very sluggish peristalsis. The barium could be expressed by hand from the stomach into the cap, but there was no voluntary emptying of the stomach. There was no organic lesion of the stomach to account for apparent obstruction. At three hours there was almost 100% retention in the stomach; at six hours there was still about 50% retention. Reëxamination four weeks later (April 25, 1955) revealed exactly the same findings as before (figure 2). At three hours the greater portion of the barium remained in the stomach. The head of the column had reached the terminal ileum. At six hours the stomach retained approximately 25% of the barium and a large amount of retained food particles. The head of the column had reached the transverse colon at six hours, and no evidence of small bowel abnormality was seen.

Regulation of the patient's diabetes remained difficult and was never completely satisfactory. Repeated stool examinations were negative for ova, parasites and occult blood, as well as for fat and striated muscle fibers. Gastric analysis revealed on one occasion 33° total acidity and 20° free acidity in 150 c.c. of withdrawn material; all specimens revealed free hydrochloric acid, without histamine. Gastroscopy on April 20, 1955, revealed moderate edema, redness and secretion, the landmarks being very distant; there was no filling defect or gross ulceration. Peristalsis started at the incisura and proceeded to prepyloric closure. The tonus changes were present in all parts of the stomach. The diagnosis was considered to be chronic gastritis. The gastric biopsy revealed normal mucosa. After the patient's first gastrointestinal series he was put on nasogastric suction with a Levin tube for three days from 8:00 p.m. to 8:00 a.m., with gastric lavage following in the morning. This preparation was followed by a second gastrointestinal series. Gastric suction and lavage were repeated several times for up to four-day periods without any objective or subjective change. His diet, in six small meals a day, was well tolerated but without effect on the x-ray findings as far as the retention of the stomach contents was concerned. Apparently he felt better on this regimen. He was given the usual maintenance support with multivitamins. During the last half of his hospitalization, the leg burns were completely healed and could no longer be considered cause for difficulty in regulating his diabetes. No hypoglycemic attacks occurred during the last third of his hospitalization.

On April 26, 1955, the patient was discharged from the hospital feeling well, with no gastrointestinal complaints and having gained three pounds. His diabetes was considered reasonably well controlled, with occasional irregular glycosuria being considered the lesser evil as compared to hypoglycemia attacks.

Case 3. This was the second Manchester Veterans Administration Hospital admission of a 43 year old white bachelor. His diabetes had been discovered in 1943 during military service. His first admission was from April 9 to April 23, 1953. At that time his regulation was difficult, and he was discharged at his own urging on a diabetic diet of 2,100 calories with 55 units of protamine zinc insulin, and was considered then to be in fairly good control. There were no complaints concerning stomach or intestines, and no gastrointestinal series was done.

The patient was admitted for the second time on April 27, 1955, and was discharged on August 15, 1955. He stated that he had been doing fairly well with the above diet and insulin until about 10 days before his second admission, when he stepped on a rusty nail and his left big toe became infected, discharging pus.

FIG. 3.

The patient was well developed and well nourished. Physical examination was within normal limits except for the left big toe, which was swollen and reddened, with several discharging sinuses and an abundant growth of granulation tissue within the injury. X-rays revealed almost complete absorption of the distal end of the distal phalanx, with marked soft tissue swelling of the entire big toe. The remaining toes showed no abnormalities. The toe was treated surgically with incision, drainage and scraping. The cultures were positive for *Staph. aureus,* and he was treated effectively, according to sensitivity tests, with Erythromycin. His blood sugar values were extremely erratic, ranging between 400 mg.% and 36 mg.%. Control of his diabetes continued to be difficult in spite of the fact that his toe was healing satisfactorily. On July 6, by which time his toe was well healed, he had a violent convulsive seizure, with hypoglycemia. Hypoglycemic reactions became more frequent, and glycosuria became erratic, and he was therefore transferred to the Medical Service (figure 3). A gastrointestinal series on June 16, 1955, revealed the esophagus to be normal. The stomach was hypotonic, with very sluggish peristalsis and poor emptying. No organic lesion was found; the duodenal cap, loop and small bowel showed no abnormalities. At three hours there was 50% retention, with the head of the meal in the ileum. At six hours the stomach was empty except for a slight trace of barium, with the head of the meal in the midtransverse colon. The repeat gastrointestinal series (figure 3) on July 8, 1955, again revealed no organic lesion. After three hours approximately 50% of the barium remained in the stomach, the head of the column having reached the lower jejunum. The gastrointestinal series (figure 3), repeated again on July 25, 1955, in comparison to the previous examination revealed some improvement in the gastric tone and peristalsis. The stomach still emptied very sluggishly, and the small bowel loops were not visualized initially. At three hours, however, the stomach was almost completely empty, with only a slight trace of barium remaining, the head of the meal having reached the ileum, and the small bowel loops showing no abnormalities. The findings were considered to be a definite improvement in the gastric function. Preceding this third gastrointestinal series the patient had been placed on nightly gastric suction. A gastric analysis on June 22, 1955, showed free hydrochloric acid to be present, 20–60–78–81 degrees. He was placed on nightly suction from 8:00 p.m. to 8:00 a.m., the contents always showing free hydrochloric acid to be present, 10–8–36 degrees on different dates. In addition, he was put on a six-meal bland diet per day, with only regular insulin according to test for eight days prior to his last gastrointestinal series. This rather strenuous regimen appeared to be quite successful, and was credited with above-cited improvement of the tonicity of the stomach by x-ray. The patient looked well at this time and felt well. There was never any complaint concerning his stomach. He complained of lack of erection but not of libido. Funduscopic examination revealed a moderate number of scattered aneurysmal hemorrhages throughout both fundi; no exudates were seen. Finally, on a diet of 2,600 calories, with 50 units of NPH and five to 10 units of regular insulin, he remained without hypoglycemic episodes; however, he was still spilling urine sugar quite erratically. This was accepted as the lesser evil, and he was discharged on this regimen. He was seen two weeks after discharge in follow-up clinic at which time his fasting blood sugar was 116 mg.%. He was feeling well, maintaining his weight and working. The final diagnoses were as follows: (1) diabetes mellitus; (2) cellulitis, left big toe, with osteomyelitis; (3) diabetic retinopathy, mild; (4) diabetic neuropathy, manifested by atony of stomach (gastroparesis diabeticorum), asymptomatic.

FIG. 3. *Case 3.* X-rays showing, in succession from left to right, the immediate, the three hour, the six hour and, if available, the 24 hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. *Upper,* June 16, 1955; *middle,* July 8, 1955; *lower,* July 25, 1955.

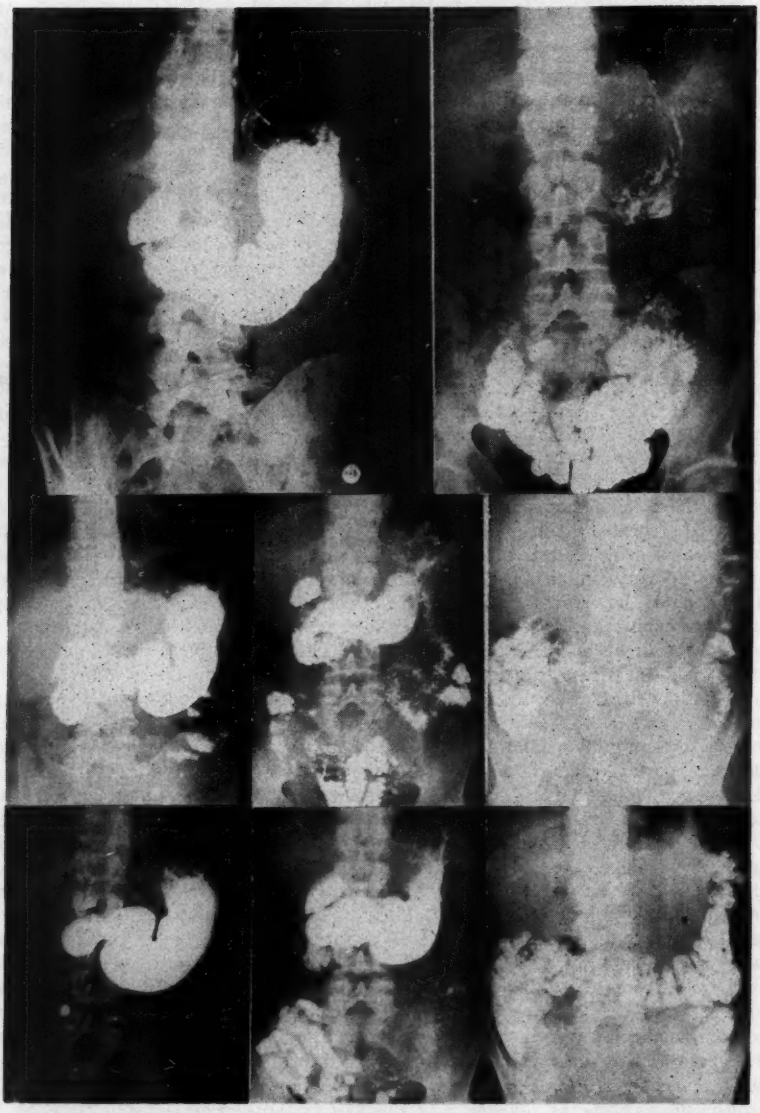

FIG. 4. *Case 4.* X-rays showing, in succession from left to right, the immediate, the three hour, the six hour and, if available, the 24 hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. *Upper,* March 28, 1955; ***middle,*** August 30, 1956; *lower,* December 10, 1956.

Case 4. A 35 year old unemployed woodworker was admitted on August 20, 1956, for the fifth time. Diabetes had been diagnosed on his first admission, in 1952. On subsequent admissions he had been treated for chronic relapsing pancreatitis with pancreatic lithiasis. On his fourth admission, in 1955, a transduodenal sphincterotomy of Oddi's sphincter was done, following which there were no further attacks of pancreatitis and pain. It is believed that his diabetes is due to the chronic pancreatitis. Figure 4 shows pancreatic lithiasis with minimal gastric residue after three hours on a previous hospitalization (March 28, 1955).

On admission in August 1956 he stated that for the last two months he had been unemployed, had stopped taking insulin, had eaten irregularly, etc., because he could not afford it. He had lost a good deal of weight, and the week before admission had had considerable vomiting.

The patient was a poorly developed and poorly nourished, weak, chronically ill young male. The physical examination was within normal limits except for obvious malnutrition and dehydration. On the vertex of the scalp and anterior to the right ear there were areas of reddened and thickened skin which appeared to be inflamed. The tongue was dry and red. His blood sugars were never elevated above 250 mg.%, and his diabetes was never a serious problem. After intravenous hydration his status slowly improved and he was soon able to tolerate a 2,400-calorie diabetic diet. His insulin was increased to 30 units of protamine zinc insulin, and his improvement continued. A gastrointestinal series on August 30, 1956 (figure 4), shows 50% retention after three hours, and shadowy remnants at six hours, but no other abnormalities. A repeat gastrointestinal series on December 10, 1956 (figure 4), revealed persistence of 50% retention after three hours and an almost empty stomach after six hours, without other abnormalities. At no time did this man complain of gastrointestinal disturbances except anorexia. His diabetes remained well controlled on 30 units of protamine zinc insulin. He maintained his weight around 115 pounds with little fluctuation. His hemoglobin averaged 12.5 gm. He continued to be a nutritional problem.

Case 5. A 47 year old white male cook and salesman was admitted on December 5, 1956. A diagnosis of diabetes had been established in 1951, at which time he was started on 40 units of NPH insulin. His insulin had been increased to 65 units within the last four months. He had noticed cold sweats, but denied major insulin reactions. He stated that he felt well but tired easily; he had noticed a lack of erection but no loss of libido. He had also noticed numbness in both feet for approximately one month, but insisted that he could walk well, the numbness appearing only when he was sitting. His weight had been fluctuating from 175 to 237 pounds; it was at present 193 pounds. His history was not otherwise remarkable, except that he freely admitted to foolish dietary indiscretions, including beer. He had had occasional bouts of diarrhea.

The patient was well built, moderately obese, and intelligent. All physiologic reflexes were present. Position and vibration senses were normal; peripheral pulses were present and equal. Physical examination was otherwise not remarkable. His eyes revealed extensive hemorrhagic areas bilaterally, with evidence of absorption and scarification. These hemorrhages showed marked improvement later. Laboratory findings showed negative tests of liver function. Blood sugars fluctuated in the 200 to 400 mg.% range. A gastrointestinal series on December 12, 1956 (figure 5) showed no abnormalities except 50% retention of a barium meal at three hours, with the head of the meal in the proximal ileum. The small bowel loops showed no abnormalities. At six hours approximately 20% of meal was in the stomach and the head of the meal in the ascending colon.

The patient's hospital course was uneventful on an 1,800 calorie diet and 55 units of NPH insulin. His diabetic control was not satisfactory but he pressed for dis-

charge, which was granted on December 28, 1956. When he was seen on follow-up six weeks later (February 1, 1957), he was feeling well, working, and maintaining his weight, but his diabetic control was still unsatisfactory. A gastrointestinal series on that date (figure 5) showed almost the same findings as the one six weeks previously except that there was somewhat less barium meal retained at three and six hours as compared to the original study.

Case 6. A 26 year old, well developed, poorly nourished young white male, employed in a crutch factory, was admitted on October 4, 1956. The patient appeared to be chronically ill. His diabetes, which had been known for only three years, had

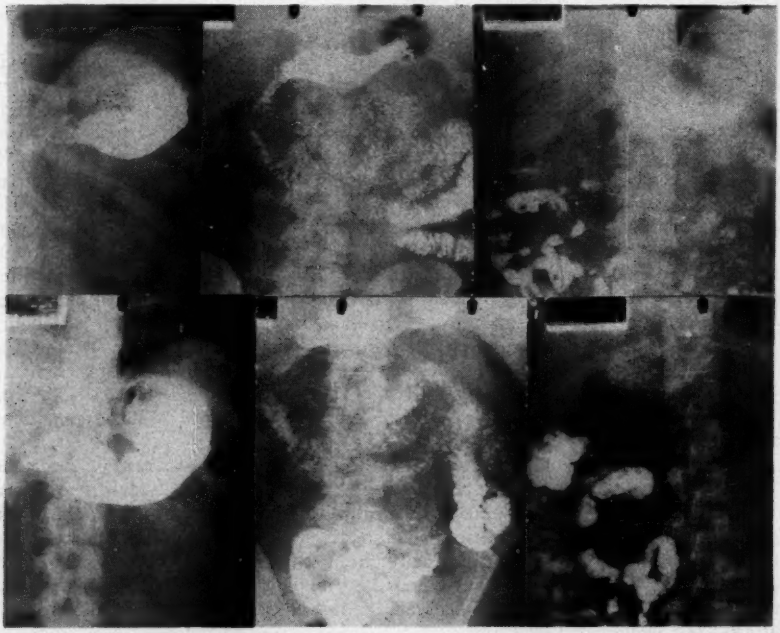

FIG. 5. *Case 5.* X-rays showing, in succession from left to right, the immediate, the three hour, and the six hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. *Upper,* December 12, 1956; *lower,* February 1, 1957.

been discovered during his service time in 1953. Since then he had been under the care of his physician. On 35 to 50 units NPH insulin and approximately a 2,400-calorie diet, his diabetes was poorly controlled. Recently he had had much difficulty in regulating his diabetes, and complained of malaise and easy fatigability.

Physical examination was entirely within normal limits. Only a slight diabetic retinopathy was found. The patient stated that he had never had any gastrointestinal symptoms whatever. A gastrointestinal series on October 12, 1956 (figure 6) revealed at three hours 80% retention of the barium meal in the stomach, with the head of the meal in the ileum. At six hours there was approximately 50% retention of the barium in the stomach, with the head of the meal in the ascending colon. No organic lesion was present. The gastric tone was only fair and peristalsis was sluggish. Gastric analysis revealed free hydrochloric acid to be present, 54 to 80°, with total acidity ranging from 64 to 95° after histamine.

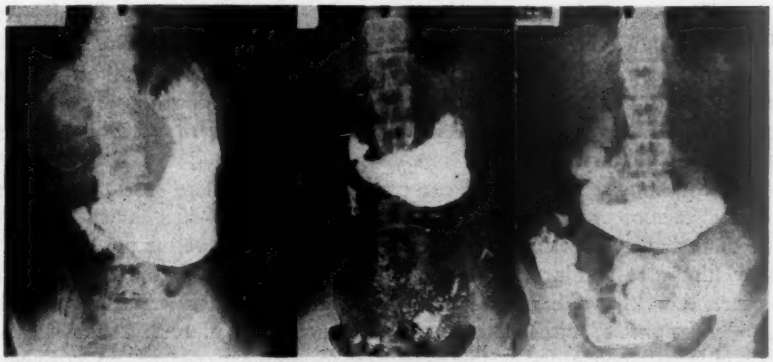

FIG. 6. *Case 6.* X-rays showing, in succession from left to right, the immediate, the three hour and the six hour exposures of gastric studies after ingestion of the x-ray meal consisting of 4 ounces of barium sulphate (Mallinckrodt) and water, q.s. to make a total of 8 ounces. October 12, 1956.

The patient was regulated with some difficulty, but remained in good control on a 2100-calorie diet, with a final dosage of 40 units protamine zinc insulin and 10 units crystalline insulin. The patient was discharged on October 26, 1956, but unfortunately he did not return for follow-up examination.

TABLE 1

Summary of Findings*

Type of Diabetes	No.	G. I. Studies		
		Normal	G. I. Pathology	Gastroparesis Diabeticorum
I Mild-Moderate	9	6	1—Duod. divertic. 1—Ulcer duod. with retention and small intest. changes 1—Gastric ulcer with retention	0 0 0
II Mod.-Severe	18	11	1—Ulcer duod. no retention	6 (33% of group)
Total	27	17	4	6 (22.2% of total)

* A total of 27 routinely admitted diabetics was studied. These cases were divided according to Joslin's criteria.[10] Group I represented the "mild to moderate" diabetics. Nine of these were examined, and six of them were found to have normal gastrointestinal series, and three showed duodenal or gastric abnormalities but no gastroparesis. Eighteen cases were classified as Group II, the "moderate to severe" diabetics. Eleven of these were found to have a normal gastrointestinal series, only one case showing duodenal pathology without retention. All of the six cases showing asymptomatic gastric retention (gastroparesis diabeticorum) were in this group. The figures give an incidence of 33% with gastroparesis for Group II, and an incidence of 22.2% for the total of 27 diabetics examined.

It is relevant to state that, of the six cases found to have gastroparesis, three showed definite diabetic retinopathy, only two had definite peripheral neuropathy, two complained of lack of erection without loss of libido, two had definite malnutrition (cases 1 and 4), three had occasional to frequent diarrhea, and only one had a period of achlorhydria.

All of these six cases revealed in their x-rays a patulous pylorus. The x-rays also showed that the gastric contents could be expressed by hand, and even some peristalsis induced and observed, without changing the retention pattern. No abnormalities of the small intestines were observed. The probability of duodenal cicatrization was ruled out by x-ray findings, as well as by careful history.

The findings seemed to indicate conclusively that these cases represented a disturbance of propulsion—specifically, of expulsion—of stomach contents. The disturbance of motor function is attributed to the vagus nerve, and the x-ray films are similar to those of gastric hypotonia after vagotomy. It appears, then, that a diabetic at some point in the progression of his diabetes may "vagotomize" himself as far as the functional motor effectiveness of his stomach is concerned. The retention of stomach contents in a diabetic obviously may cause confusion as far as food intake and utilization are concerned.

Our attempts at treatment were uniformly unsuccessful. We believed that continuous or fractionated gastric suction, including lavage, as well as the six-small-meal diet, in combination with crystalline insulin alone, did more to improve diabetic control and alleviate the retention than the use of medication including Urecholin or Mecholyl, to mention two. The effectiveness of vitamin supplements, including vitamin B_{12}, remains obscure in connection with the retention.

This gastric retention in diabetics was not known, or at least was described, in the pre-insulin era, which unfortunately coincides roughly with the pre-roentgen era. There are references to retention, with wide-open pylorus considered to be due to "nervous reasons" dating back to Kussmaul and Bouchard.[11] The term "gastroparesis" was used by von Bergmann, Katsch and Kuttner, among others, intermixed with terms like "gastric atony" and "pyloric insufficiency," but only in connection with ulcer disease, duodenal and gastric, where no direct anatomic connection could explain the gastric retention or the wide-open pylorus.[12] The only significantly recurring mention of gastric retention in diabetics occurs together with other debilitating diseases, which include tuberculosis, typhus, tabes dorsalis, etc.[13]

The present etiologic concept of diabetic neuropathy is summed up by Marble: "Neuropathy results from the abnormal metabolism of unregulated diabetes." [1] No etiologic role could be attributed to anemia, alcohol, dietary insufficiencies, drugs, infections or lead poisoning in the large, controlled material of the Joslin Clinic (Marble).[1] There is general agreement that the appearance of neuropathy is usually preceded by a period of an uncontrolled or insufficiently controlled diabetic state.

This asymptomatic gastric retention appears to occur in "young" diabetics (those whose disease has been known for from three to 12 years), and coinciding with their use of the long-acting insulins. The probability that the long acting-insulins, especially the metal zinc, may be a causative

factor presents itself. It is known that zinc administered parenterally to experimental animals results in serious symptoms.[14] Since zinc has been proved to be part of the molecule of the enzyme carbonic anhydrase, and essential to its function,[15] it has assumed an importance similar to that of iron in hemoglobin, zinc being essential for the exchange of CO_2.[16] In this connection, it appears that further progress in enzyme chemistry might help to solve the baffling problems of diabetic neuropathy and to define further the role of zinc which, in addition to its natural ubiquitous occurrence, is present in cosmetics, deodorants, antiperspirants, etc., which are used by everybody, including diabetics.[16]

In our cases, it appears that the onset of gastric retention in diabetics is insidious, masked and without any definite symptoms. It occurs in anorexic, diarrheal diabetics with manifest neuropathy, as well as in those who have no symptoms other than their uncontrolled diabetes. We do not know the time of onset, the duration or the cure of this diabetic gastric retention.

Our cases are few in number, but even allowing for simple coincidence, I believe the findings worthy of attention. The observed gastric hypotonia represents disturbed physiology and appears to be a part of diabetic neuropathy involving the autonomic nervous system, and it may adversely influence the satisfactory treatment of diabetes. I believe that this syndrome —gastroparesis diabeticorum—is more often overlooked than diagnosed, and I propose that the search for this syndrome in diabetics should be made as much a clinical routine as the search for other manifestations of the metabolic disturbance we know as diabetes mellitus.

Acknowledgment

I am indebted to George D. Krasner, M.D., Chief, Radiology Service, for his advice and coöperation and to Dr. Patrick J. FitzGerald and Dr. Samuel L. Cohen, Medical Service, for their support.

Summario in Interlingua

Iste studio esseva motivate per le discoperta incidental de sever asymptomatic retention gastric in un patiente diabetic. Il es cognoscite que disturbationes gastrointestinal, manifeste in un accelerate o prolongate passage via le intestinos, pote accompaniar le symptomas de diabete. Iste disturbationes esseva recognoscite como effecto del dysfunction del systema nervose autonome.

Vinti-septe diabeticos esseva studiate in duo gruppos. Gruppo I—"leve a moderate"—consisteva de nove casos. In sex, le aspecto de un roentgeno-serie gastrointestinal esseva normal; in le tres alteres, illo indicava le presentia de lesiones gastric o duodenal sin asymptomatic retention gastric. Gruppo II—"moderate a sever"—consisteva de 18 casos. Un monstrava ulcere duodenal. In 11, le roentgeno-series gastrointestinal esseva normal. Le remanente sex casos in iste gruppo habeva asymptomatic retention gastric (gastroparesis de diabeticos). Assi le incidentia de gastroparesis esseva 33% in le gruppo con diabete moderate a sever e 22,2% in le serie total de 27 diabeticos. Omne le sex habeva retention gastric de 50% o plus post tres horas sin symptomatologia clinic; tres habeva retention gastric de 25 a 50% post sex horas; duo de iste tres habeva retention gastric de 15 a 30% post 24 horas.

Nostre constatationes indica que iste casos representa disturbationes del propulsion—specificamente, del expulsion—del contento gastric, con un pyloro allargate simile a lo que es trovate post vagotomia. Iste syndrome, que non esseva cognoscite durante le era pre-insulinic, es asymptomatic. Su declaration e su curso es insidiose e mascate e occurre in diabeticos anorexic e diarrheic qui usa insulina a action prolongate e ha "neuropathias" manifeste como etiam in patientes qui ha nulle symptomas foras de un non-regulate diabete. Le tempore del declaration, le duration, e le therapia de iste syndrome non es cognoscite. Nos suppone que le causa es un infringimento del nervo vage. Viste le importantia que le metallo zinc ha disveloppate in le chimia del enzymas, le possibilitate es signalate que le insulinas a action prolongate constitue un factor etiologic.

Le complexo de iste constatationes es digne de attention mesmo si on vole explicar los in parte como simplemente un coincidentia. Le constatationes suggere que iste hypotonia gastric (gastroparesis de diabeticos) es un parte de un neuropathia diabetic que affice le nervo vage e in plus que illo exerce possibilemente un influentia adverse super le tractamento de diabete.

Le syndrome de gastroparesis de diabeticos escappa al diagnose in le majoritate del casos. Pro iste ration, il es recommendate que su presentia es investigate routinarimente in le mesme maniera como altere manifestationes de diabete.

BIBLIOGRAPHY

1. Marble, A., *in* Joslin, E. P., Root, H. F., White, P., and Marble, A.: The treatment of diabetes mellitus, 9th Ed., 1952, Lea & Febiger, Philadelphia, pp. 480–481 and 485.
2. Wood, M. N.: Chronic peptic ulcer in ninety-four diabetics, Am. J. Digest. Dis. **14**: 1–11, 1947.
3. Quigley, J. P.: Gastric motility and evacuation, *in* Peptic ulcer, edited by David T. Sandweiss, 1951, W. B. Saunders Co., Philadelphia, p. 75–81.
4. Rundles, R. W.: Diabetic neuropathy, Medicine **24**: 111–160, 1945.
5. Hodges, F. J., Rundles, R. W., and Hanelin, J.: Roentgenologic study of small intestine. II. Dysfunction associated with neurologic diseases, Radiology **49**: 659–673, 1947.
6. Golden, R., and Lepore, M. J.: Syndrome due to deficiency of vitamin B complex, J. A. M. A. **117**: 918–923, 1941.
7. Martin, M. M.: Diabetic neuropathy, a clinical study of 150 cases, Brain **76**: 594–624, 1953.
8. Golden, R.: Diagnostic roentgenology, Vol. 1, 1948, Thomas Nelson, New York, p. 340G.
9. Moore, F. D., Chapman, W. P., Schultz, M. D., and Jones, C. M.: Transdiaphragmatic resection of vagus nerves for peptic ulcer, New England J. Med. **234**: 241–251, 1946.
10. Joslin, E. P., *in* Joslin, E. P., Root, H. F., White, P., and Marble, A.: Diabetes mellitus, 9th Ed., 1952, Lea & Febiger, Philadelphia, p. 97.
11. Katsch, G., *in* von Bergmann, G., and Staehelin, R.: Handbook of internal medicine, 2nd Ed., 1926, Julius Springer, Berlin, pp. 522–527.
12. Schlesinger, E.: Chronische Gastroparese als Ursache schwerer motorischer Insufficienz bei freiem Pylorus, Mitt. a. d. Grenzgeb. d. med. u. Chir. **32**: 30, 1920.
13. Boas, T.: Disease of the stomach, 9th Ed., 1925, Georg Thieme, Leipzig, p. 200.
14. Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics, 1947, The Macmillan Co., New York, pp. 760–761, 860–861.
15. Keilin, D., and Mann, T.: Carbonic anhydrase, Biochem. J. **34**: 1163–1176, 1940.
16. Vallee, B. L.: Metabolic role of zinc, J. A. M. A. **162**: 1053–1057, 1956.

THE CLINICAL SIGNIFICANCE OF LACTIC DEHYDROGENASE ACTIVITY OF SEROUS EFFUSIONS *

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Introduction

Observations from tissue culture studies suggest that malignant neoplastic cells contribute increasing amounts of lactic dehydrogenase (LD) activity to the fluid medium which bathes the cells.[1] Similar activity by cancer cells in vivo is implied by observations made of LD activity in the serum and the peritoneal fluid of mice with Ehrlich's ascites carcinoma.[2] The generalization that malignant tissue contributes LD activity to fluids which bathe them is implied clinically by the fact that LD activity of cerebrospinal fluid is increased above the normal range in spinal fluid specimens obtained from patients with cancer, lymphoma and leukemia.[3]

Pleural and peritoneal effusions containing malignant cells may be conceived of as in vivo cultures of cancer cells. It is postulated that the malignant cells in and about the serous effusions may contribute LD activity to the encapsulated extracellular fluid. The enzyme activity of LD in an effusion associated with non-neoplastic disease states is consistently lower than the LD activity of the plasma and serum derived from the same individuals. Inasmuch as the globulin fraction of an effusion does not exchange readily with the plasma constituent, and LD activity is primarily a globulin component, it appeared likely that serous effusions containing malignant cells would have a greater LD activity than would the LD of the serum derived from the same individual.

The purpose of this report is to present the findings of LD activity in serous effusions, and to contrast the enzyme activity of the fluid with the LD activity of the serum obtained from the same individual. The enzyme studies were then compared with the results of cytologic, cell block and other examinations of the respective effusions.

Methods and Materials

The patients studied were seen at Memorial Hospital, James Ewing Hospital, and The Brooklyn Hospital. Not included are patients who received either systemic intrapleural or intraperitoneal chemotherapy for neo-

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plasia or radiation therapy to the serous cavity prior to sampling of the serous effusion. Pleural and peritoneal effusions were obtained by the usual technic of thoracentesis and paracentesis, respectively. The effusion was sampled in each case so that individual specimens were examined for erythrocytes, leukocytes, protein, cytologic flora by the Papanicolaou method and by the cell block technic, and LD activity. The samples for enzymatic determination were centrifuged at 3000 rpm for 20 minutes; grossly hemo-

TABLE 1

Comparison of the LD activity of pleural or peritoneal fluid and serum obtained by thoracentesis or paracentesis and venipuncture, respectively, at about the same hour from patients with non-neoplastic disease states. In each instance the cytologic examination and/or cell block study of the serous fluid was negative for malignant cells.

Patient	Clinical Diagnosis	Site of Serous Effusion	Serum LD	Serous Effusion LD
Bla	Nephrosis	Abdominal	400	40
Due	Nephrosis	Abdominal	750	35
Han	Nephrosis	Abdominal	740	52
		Pleural	740	44
Pan	Nephrosis	Abdominal	440	30
Bru	Chronic glomerular nephritis	Pleural	1,630	300
Bar	Laennec's cirrhosis	Abdominal	400	100
Cha	Laennec's cirrhosis	Abdominal	410	80
Hag	Laennec's cirrhosis	Abdominal	800	360
Ott	Laennec's cirrhosis	Abdominal	420	240
Pet	Laennec's cirrhosis	Abdominal	440	420
		Abdominal	400	360
Tho	Myxedema	Pleural	440	300
		Abdominal	420	320
		Pleural	760	220
Mah	Congestive heart failure	Pleural	480	260
Mil	Congestive heart failure	Pleural	480	230
Pen	Congestive heart failure	Pleural	1,000	360
		Pleural	980	310
Rog	Congestive heart failure	Pleural	850	300
Sal	Congestive heart failure	Pleural	440	120
Qua	Congestive heart failure	Pleural	420	320
Lin	Congestive heart failure	Pleural	280	240
Fio	Pulmonary tuberculosis	Pleural	330	220
Lam	Pulmonary tuberculosis	Pleural	600	360
Mar	Pulmonary tuberculosis	Pleural	720	360
Mah	Pneumonitis, cause undetermined	Pleural	380	34

lyzed specimens were discarded. The presence of yellow pigmentation, gross blood or other discoloration was not considered reason for rejection of the specimen. The supernatant was used for enzyme determination, which was performed within 12 hours after the specimen was collected. Within the hour of the thoracentesis or paracentesis, a venous blood sample was obtained without regard to the fasting state, and the serum was separated. Both the serum and effusion LD activity were determined spectrophotometrically by the method previously described, using 0.2 ml. of the respective fluid.[4] Duplicate results agreed within 15%.

Results

Table 1 compares the LD activity of 27 specimens of pleural or peritoneal fluid and serum obtained by thoracentesis or paracentesis and venipuncture, respectively, from 22 patients with serous effusions due to nonneoplastic disease states. Cytologic and cell block study of the cellular flora of the serous fluids failed to disclose the presence of abnormal or malignant cells. In all instances listed the LD activity of the serous effusion is less than the corresponding serum LD activity. Except in fluid obtained from patients with nephrosis, in which the LD activity of the effusion was less than 60 units, no relation between disease state and effusion LD activity was noted. Table 2 contrasts the LD activity of 26 specimens of pleural fluid and serum obtained by thoracentesis and venipuncture, respectively, from 21 patients with pleural effusions associated with malignant neoplastic disease states. In every instance the cytologic examination and/or the cell block study of the cellular constituents of the pleural fluid revealed abnormal and/or malignant cells. In each of these cases the LD activity of the malignant effusion significantly exceeds that of the patient's blood serum.

Table 2

Comparison of the LD activity of pleural fluid and serum obtained by thoracentesis and venipuncture, respectively, at about the same hour from patients with lymphomatous and carcinomatous disease states. In each instance the cytologic examination and/or cell block study of the pleural fluid was positive for malignant cells.

Patient	Clinical and/or Pathologic Diagnosis	Serum LD	Pleural Fluid LD	
Abr	Adenocarcinoma of lung	750	860	Specimen 1
		350	800	Specimen 2
		380	550	Specimen 3
		740	880	Specimen 4
		320	530	Specimen 5
Bac	Lymphosarcoma	2,400	2,600	
Bar	Infiltrating duct, carcinoma of breast	430	1,800	
Ben	Adenocarcinoma of breast	520	900	
Ber	Neuroblastoma	1,920	3,600	
Bla	Adenocarcinoma, primary site unknown	480	760	
Com	Infiltrating duct, carcinoma of breast	560	1,920	
Cay	Epidermoid carcinoma of lung	460	1,260	
Dan	Adenocarcinoma of stomach	800	1,050	
Dib	Duct cell carcinoma of breast	330	630	
Hah	Epidermoid carcinoma of lung	360	520	
Hem	Papillary adenocarcinoma of ovary	300	440	
Ken	Adenocarcinoma of breast	380	1,440	
Kev	Epidermoid carcinoma of lung	720	1,000	Specimen 1
		1,000	1,400	Specimen 2
Kol	Adenocarcinoma of breast	540	1,010	
Lis	Adenocarcinoma of pancreas	220	340	
Oli	Adenocarcinoma, primary unknown	680	840	
Ship	Hodgkin's disease	1,620	2,880	Specimen 1
		1,500	3,240	Specimen 2
Sol	Adenocarcinoma of breast	360	580	
Ste	Squamous carcinoma of esophagus	1,300	1,900	
Val	Reticulum cell sarcoma	780	1,860	Specimen 1
		760	1,680	Specimen 2

TABLE 3

Comparison of the LD activity of pleural or peritoneal fluid and serum obtained by thoracentesis or paracentesis and venipuncture, respectively, at about the same hour from patients with lymphomatous and carcinomatous disease states. In each instance the cytologic examination and/or cell block study of the serous fluid was negative for malignant cells.

Patient	Clinical and/or Pathologic Diagnosis	Serum LD	Serous Effusion LD	Site
Bat	Hodgkin's disease	920	630	Pleural
Def	Lymphosarcoma	180	150	Pleural
Lub	Primary carcinoma of liver	560	220	Pleural
Lue	Malignant melanoma	860	220	Pleural
		480	290	Abdominal
Raf	Lymphosarcoma	540	350	Pleural
Sch	Adenocarcinoma of breast	960	340	Abdominal
Swa	Lymphosarcoma	480	280	Abdominal
Zep	Adenocarcinoma of breast	740	200	Pleural

In neither group of patients studied was a consistent relationship noted between LD activity of the effusion and the specific gravity, erythrocyte and leukocyte count, and protein content of the fluid.

Ten pleural effusions obtained from eight patients with malignant neoplastic disease were found on cytologic and cell block study to be devoid of abnormal and malignant cells. Table 3 compares the LD activity of the pleural fluid and the respective serum LD activity in this group of patients with lymphomatous and carcinomatous disease. In each instance the serum LD was greater than the activity of the pleural fluid.

Table 4 compares the LD activity of pleural fluid and serum obtained by thoracentesis and venipuncture, respectively, from another group of patients with neoplastic and non-neoplastic disease states. In each instance the cytologic examination and cell block study of the serous fluid were negative for abnormal and malignant cells. An autopsy of a 17 year old patient (Hol) revealed the right pleural surface to be smooth and glistening except at the apex, which was marked by an irregularly ovoid, gray, white, firm tumor 5 cm. in greatest diameter, extending into the adjacent wall of the

TABLE 4

Comparison of the LD activity of pleural fluid and serum obtained by thoracentesis and venipuncture, respectively, at about the same hour from patients with neoplastic and non-neoplastic disease states. In each instance the cytologic examination and cell block study of the serous fluid were negative for malignant cells, while the LD activity of the effusion was greater than the serum LD activity.

Patient	Clinical and/or Pathologic Diagnosis	Serum LD	Pleural Effusion LD
Goo	Hodgkin's disease	1,200	1,920
Hol	Hodgkin's disease	480	500
Joh	Pulmonary tuberculosis	460	820
		480	800
Ols	Duct cell carcinoma of breast	300	340

thorax. Microscopic sections showed Hodgkin's granulomatous tissue involving the lung and pleura and including the pleural surface. Patient Job had a sputum specimen positive on culture for tubercle bacilli. There was no clinical evidence to suggest the presence of pulmonary or other neoplasia. At the time the two pleural effusions were collected, the patient was receiving streptomycin, para-aminosalicylic acid, and isonicotinic acid hydrazide. Three other patients (table 1) with pleural effusions associated with pulmonary tuberculosis, but not on chemotherapy at the time of the thoracentesis, had serum LD activity greater than the LD of the pleural fluid. In one patient (Lam) the pleural fluid culture was positive for tubercle bacilli. Patient Ols had duct cell carcinoma of the breast, and the histologic diagnosis was confirmed. Patient Goo died but was not autopsied; at the time of the thoracentesis and at the time of the death, Hodgkin's disease was widely disseminated and involved bone, liver, spleen, lymph nodes, lung, pleura and pericardium.

Discussion

There is evidence obtained using tritium-labeled water to suggest that the water content of ascitic fluid enters and leaves a serous cavity at a very rapid rate. This implies that serous effusions are rapidly circulating media rather than a segregated reservoir.[5] However, the globulin constituent of serous fluid tends to reach equilibrium with that of the plasma at a rate considerably slower than water and much slower than albumin. With the use of C^{14}-labeled protein, it has been demonstrated in the dog that the rate of transfer of globulin across the serous membrane is three times slower than that of albumin, and that it takes globulin two or more days to reach equilibrium with the same component in the plasma.[6] LD activity is a constituent of plasma globulin and presumably is a globulin constituent of the effusion protein.[7] This would suggest that the globulin fraction—and therefore the LD activity of an effusion—does not come into equilibrium with the plasma globulin and plasma or serum LD activity as long as ascites is being actively produced, or as long as LD is being added to the effusion.

Pleural and peritoneal effusions associated with non-neoplastic disease states such as congestive heart failure and cirrhosis have enzyme activities less than the respective serum enzyme activity. Table 5 contrasts the LD, glutamic-oxalo-acetic transaminase, glutamic-pyruvic transaminase, amylase, alkaline phosphatase and acid phosphatase activities of serous fluid with the respective enzyme activities of the serum obtained from patients with neoplastic and non-neoplastic disease states. The cytologically negative fluids obtained from patients with neoplastic and non-neoplastic diseases had LD and other enzyme activities less than the respective serum enzyme activities. The effusions containing malignant cells had LD activity greater than the serum LD, but the other serous fluid enzymes were of lower activity than the respective serum enzyme activities. These observations suggest

that the greater LD activity than serum LD in instances of cytologically malignant effusion is characteristic of LD and perhaps other enzymes as well, but not of enzyme activities in general. Whether the non-neoplastic cellular elements of serous effusions contribute any LD activity to the fluid is not entirely clear; however, whatever activity is thereby added is not sufficient to bring the LD activity of the serous effusion above that of the corresponding serum.

TABLE 5

Comparison of various enzyme activities of pleural fluid and serum obtained by thoracentesis and venipuncture, respectively, at about the same hour from patients with neoplastic and non-neoplastic disease states. The cytologic and cell block examination of the serous fluid is described as positive (+) or negative (−) for malignant cells. (Fld = serous effusion, GO-T = glutamic oxalo-acetic transaminase, GP-T = glutamic pyruvic transaminase.)

Pt.	Clinical and/or Pathologic Diagnosis	LD		GO-T		GP-T		Amylase		Alk. P'ase		Acid P'ase		Cytology Smear	Cell Block
		Serum	Fld.	Serum	Fld.	Serum	Fld.	Serum	Fld.	Serum	Fld.	Serum	Fld.		
		units/ml.		units/ml.		units/ml.		units/ 100 ml.		units/ 100 ml.		units/ 100 ml.			
Abr	Adenocarcinoma of lung	320	520	22	18	26	8	65	52	6.2	1.4	0.72	0.0	+	+
Bac	Lymphosarcoma	2,400	2,600	120	64	77	26	40	19	3.2	0.58	0.13	0.0	+	+
Bar	Infiltrating duct, carcinoma of breast	430	1,800	51	38	38	14							+	+
Zep	Adenocarcinoma of breast	1,200	260	53	12	60	7	54	41	7.4	2.5	0.11	0.00	−	−
Bar	Hodgkin's disease	920	630	22	6	39	19							−	−
Qua	Congestive heart failure	420	320	24	6	24	6	64	44	3.3	0.69	0.28	0.04	−	−
Rog	Congestive heart failure	850	300	35	35	18	16	60	30	5.2	1.2	0.10	0.00	−	−
Sal	Congestive heart failure	440	120	16	14	32	12	40	18	4.0	0.38	0.20	0.00	−	−
Hag	Laennec's cirrhosis	800	360	42	24	27	10	45	15	3.8	1.2	0.10	0.00	−	−
Ott	Laennec's cirrhosis	420	240	46	20	24	12	50	10	4.2	1.6	0.00	0.00	−	−

Both in vitro and in vivo studies previously cited suggest that in the absence of tissue and/or cellular necrosis, malignant cells contribute LD activity to the medium which bathes the neoplastic tissue. Serous effusions containing exfoliated but viable malignant cells are probably being enriched with LD exudated from the suspended cells. However, serous fluid free of exfoliated cells but nevertheless bathing pleural or peritoneal implants of malignant tissue would be expected to be enriched with LD by the contiguous malignant tissue. On the basis of this reasoning, one may expect the LD of effusions to be greater than the serum LD activity in serous fluids containing malignant cells, as well as in those fluids bathing malignant tissue but free of exfoliated neoplastic cells. Accordingly, effusion LD activity is a reflection of malignant tissue in contact with a serous surface and usually —but not necessarily—able to be correlated with the malignant cytologic constituents of the fluid. Therefore, the findings of the cytologic examina-

tion and of the enzymatic activity of a serous effusion from a patient with lymphomatous or carcinomatous disease are two related but nevertheless potentially independent expressions of malignant neoplasia within a serous cavity.

It is not within the province of this presentation to assess the reliability of identification of malignant cells in effusions. However, it is pertinent to point out that in a study by a competent cytologist, interpreting without knowledge of the clinical facts, 10% of positive malignant interpretations of cellular constituents of serous fluids were found to be incorrect.[8] The reliability of the enzymatic approach to the diagnosis of malignant cellular constituents of serous effusions cannot be assessed from the relatively small number of examinations herein reported. However, one patient with pulmonary tuberculosis had enzymatic findings consistent with intrapleural neoplasia in the absence of clinical or cytologic evidence of malignancy. Although no leukocyte count was obtained on the pleural fluid obtained from the tuberculous patient (Joh), it is not uncommon in effusions associated with tuberculosis to find a preponderance of lymphocytes. Whether the lymphocytic flora of the pleural fluid from the tuberculous patient accounted for the misleading enzymatic findings must remain conjectural.

The number of exfoliated abnormal or malignant cells which are necessary in a serous fluid in order to permit cytologic detection is difficult to assess. In 45% of the effusions associated with lymphosarcoma and lymphatic leukemia, an abnormal cellular picture was present. Cells diagnostic of granulocytic leukemia were present in about 65% of the effusions with this disease state. In one reported series, in none of the effusions associated with Hodgkin's disease were definitely abnormal cells present.[9] Others have noted abnormal cells in serous effusions associated with Hodgkin's disease.[10] In carcinoma involving serous cavities, the concentration of exfoliated cells necessary in the fluid in order to permit the cells to be found and identified on a smear or specimen of cell block is uncertain. It would therefore appear that a fluid bathing or containing a relatively sparse number of malignant cells may appear cytologically negative if the number of exfoliated cells does not exceed the threshold for detection by the usual cytologic and/or cell block technics. Whether these speculations explain the discrepancy between cytologic and enzymatic findings of the effusions from the three of the four patients described in table 4 is unclear.

If an effusion is chylous and therefore derived primarily from chyle rather than from plasma, the comparison of LD activity of the effusion with LD activity of serum is not informative. In one patient (For) with lymphatic leukemia and adenocarcinoma of the rectum, both pleural and peritoneal effusions contained malignant cells but had a lower LD activity than did the serum (serum LD = 290 units/ml.; pleural effusion LD = 220 units/ ml.; peritoneal effusion LD = 200 units/ml.). Although a cytologically uncontaminated chyle specimen could not be obtained from this

patient, a chyle specimen was obtained at operation from another patient. The LD activity of the chyle was half that of the serum of the same patient. Accordingly, chylous effusions cannot be included in the enzymatic identification of effusions unless a chyle sample from a lymphatic channel is obtainable for comparison.

Intrapleural and intraperitoneal fluids may occur which cannot accurately be described as effusions. These fluids are in fact cystic tissue debris which finds its way into the serous cavity. A patient (Rog) with recurrent necrotizing pancreatitis and pseudocyst formation was found to have dark greenish brown fluid in the right pleural space. The LD activity of the fluid was 2,200 units/ml., and that of the serum, 500 units/ml. The pleural fluid amylase was 519 units, while that of the serum was 329 units. At autopsy, the patient was found to have chronic pancreatitis with pancreatic cyst formation secondary to chronic pancreatitis. In addition, there was right fibrinopurulent pleuritis. It appeared that the right pleural fluid was pancreatic tissue debris which dissected into the pleural space, and that, in fact, the pleural fluid was not an effusion but cystic pancreatic fluid and secretions; this was reflected in the high pleural fluid amylase and incidentally high LD activity. In another instance, chocolate brownish peritoneal fluid was removed at laparotomy from another patient (Mar). The LD activity of the fluid was 7,000 units/ml., while that of the serum was 3,800. It was quite clear to the surgeon that the fluid within the peritoneal space was not exudate or transudate, but rather fluid from a large ovarian cyst. It would therefore appear that if the fluid examined enzymatically is not in fact a pleural or peritoneal effusion, the generalization regarding LD activity cannot be relied upon for differentiation of malignant from benign fluids derived from cysts and liquid tissue debris.

Only one pericardial effusion was examined. The fluid was obtained from a 59 year old male (Lor) who had bronchogenic carcinoma associated with a massive pericardial effusion. The serous fluid contained malignant cells on smear and cell block study. The serum LD was 1,200 units/ml., while the LD activity of the pericardial fluid was 2,800 units/ml. Twenty milligrams of nitrogen mustard were subsequently instilled into the pericardial sac, but the patient died 14 hours later and no autopsy was obtained. No opportunity was afforded to examine fluid from empyema, but it is to be expected that purulent chest fluid would have a higher LD than serum LD activity, presumably because of the large component of leukocytes and tissue debris.

All of the fluids from patients with malignant disease were obtained when the patients were not on radiation or chemical or hormonal treatment for lymphoma or cancer. Preliminary observations suggest that hormonal treatment in breast cancer, nitrogen mustard therapy in lymphomata, and radiation therapy in both types of disease states may result in enzymatic change in serous fluids, with or without change in cytologic flora. In

several instances pleural fluids which were cytologically positive but enzymatically negative while the patients with breast cancer were on hormonal treatment became enzymatically positive for malignancy when the hormonal treatment was discontinued. Further study is necessary to determine the effect of treatment on the enzymatic behavior of the cancerous and lymphomatous cells in serous effusion. Without eradicating malignant cells from an effusion, a therapeutic agent may influence the metabolic and/or enzymatic behavior of malignant cellular constituents of an effusion. This paradox between histologic character and enzymatic behavior of cancer is well recognized in prostatic cancer influenced by estrogen and reflected in serum acid phosphatase alterations.

Further study of LD activity and other enzymatic flora of serous effusions is necessary before a definitive conclusion can be reached regarding the reliability of the chemical technic for the characterization of effusions as either cytologically benign or malignant. The confusion contributed by non-neoplastic cellular elements such as mesothelial cells and histiocytes and other constituents of serous fluids in the identification of malignant cells is generally recognized.[10] An enzymatic technic which would complement cytologic examination of serous fluids would fill a genuine need.

Summary

1. Malignant neoplastic cells in vitro and in vivo have been shown to contribute LD activity to the fluid medium which bathes the cellular elements.

2. Pleural and peritoneal effusions containing or in contact with malignant cells and/or tissue have LD activity greater than the plasma (or serum) from which the serous fluids are derived.

3. Serous effusions obtained from patients without neoplastic disease are found to have LD activity lower than the plasma (or serum) from which the effusions are derived.

4. The clinical variations and implications of these generalizations are discussed in light of employing the enzymatic technic for the diagnosis of effusions containing malignant cells.

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Summario in Interlingua

Effusiones pleural e peritonee que contine cellulas maligne pote esser reguardate como culturas in vivo de cellulas de cancere. Es postulate que le cellulas maligne in e circa le effusiones serose pote contribuer activitate de dishydrogenase lactic (DL) al incapsulate fluido extracellular. Le activitate enzymatic de DL in un effusion associate con non-neoplastic statos pathologic es uniformemente inferior al activitate

enzymatic de DL in le plasma e le sero obtenite ab le mesme individuo. Viste que le fraction globulinic de un effusion non se excambia facilemente con le constituente plasmatic (e le activitate de DL es primarimente le affaire de un componente globulinic), il pareva probabile que effusiones serose continente cellulas maligne habera un plus grande activitate de DL que le sero obtenite ab le mesme individuo.

Le objectivo del presente reporto es listar le magnitudes del activitate de DL in effusiones serose e contrastar los con le magnitudes del activitate de DL in sero obtenite ab le mesme individuo. Le resultatos de iste studios enzymatic esseva subsequentemente comparate con le resultatos de examines cytologic e altere formas de examine del effusiones respective.

Esseva monstrate que effusiones pleural e peritonee que contine maligne cellulas e/o histos o se trova in contacto con tales ha plus grande activitate de DL que le plasma (o le sero) ab que le fluidos serose esseva derivate. Effusiones serose obtenite ab patientes sin morbo neoplastic exhibiva un plus basse activitate de DL que le plasma (o le sero) ab que le effusiones esseva derivate. Le variationes clinic de iste generalisationes e le consequentias inherente in illos es discutite con referentias al uso del technica enzymatic in le diagnose de effusiones que contine cellulas maligne.

BIBLIOGRAPHY

1. Wróblewski, F., and Moore, A. G.: Unpublished observations.
2. Friend, C., and Wróblewski, F.: Unpublished observations.
3. Wróblewski, F., Decker, B., and Wróblewski, R.: The clinical significance of alterations in lactic dehydrogenase activity in spinal fluid, N. Eng. J. Med., in press.
4. Wróblewski, F., and LaDue, J. S.: Lactic dehydrogenase activity in blood, Proc. Soc. Exper. Biol. and Med. **90**: 210–213, 1955.
5. Prentice, T. C., Siri, W., and Joiner, E. E.: Quantitative studies of ascitic fluid circulation with tritium-labeled water, Am. J. Med. **13**: 668–673, 1952.
6. McKee, F. W., Yuile, C. L., Lawson, B. G., and Whipple, G. H.: Albumin and globulin circulation in experimental ascites, J. Exper. Med. **95**: 161–172, 1952.
7. Wróblewski, F., and Korngold, L.: Unpublished observations.
8. Foot, N. C.: Identification of cells in exudates and effusates, Ann. New York Acad. Sc. **63**: 1324–1330, 1956.
9. Luse, S. A., and Reagan, J. W.: A histiocytologic and electron microscopic study of effusions associated with malignant disease, Ann. New York Acad. Sc. **63**: 1331–1347, 1956.
10. Foot, N. C.: Identification of types and primary sites of metastatic tumors from exfoliated cells in serous fluids, Am. J. Path. **30**: 661–677, 1954.

DETERMINATION OF C-REACTIVE PROTEIN IN THE BLOOD OF PATIENTS WITH HODGKIN'S DISEASE*

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SINCE the first description of C-reactive protein by Tillett and Francis in 1930, the occurrence of this substance, which is not present in the blood of normal individuals, has been noted by many workers in a wide variety of disorders.[1-4] The first extensive clinical study of C-reactive protein in a specific disease was that of Anderson and McCarty, who found, in a group of 45 patients with acute rheumatic fever, that the determination for this acute phase protein provided a sensitive and useful index of the activity of the disease process.[5] Their findings have since been confirmed by other groups, and the test for C-reactive protein is now one of the established laboratory tests used in the diagnosis and management of rheumatic fever.[6, 7, 8] Although several extensive screening studies of patients with diseases other than rheumatic fever have been carried out, intensive serial observations of the C-reactive protein have been confined to patients with only a few such diseases. The most notable of these diseases are myocardial infarction and coronary insufficiency.[9, 10]

It has been reported previously that pathologic fluids obtained from patients with generalized Hodgkin's disease contain large amounts of C-reactive protein.[11] Indeed, laboratories concerned with the preparation of crystalline C-reactive protein for use as an antigen or for physicochemical characterization of the substance have found the most consistently satisfactory source of material to be chest and abdominal fluids obtained from patients with Hodgkin's disease. Large amounts of C-reactive protein are not consistently found in pathologic fluids obtained from patients with other malignant tumors.[12] The present study is concerned with the use of the C-reactive protein determination as a possible indicator of disease activity in patients with Hodgkin's disease.

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Materials and Methods

Case Material: One hundred twenty-one patients with Hodgkin's disease proved by biopsy were studied over a period of 14 months. All but 15 of them were patients of the Medical Neoplasia Service of Memorial Center. The other 15 patients followed closely with frequent serial bleedings to determine the effect of different methods of treatment on the C-reactive protein were patients on the Medical Service of The Mount Sinai Hospital.

The diagnostic criteria of Hodgkin's disease used in this study were those of Jackson and Parker, liberally interpreted.[13] All cases studied were classified into one of three types: paragranuloma, granuloma and sarcoma. In some instances the pathologic picture was mixed. For instance, in several patients who had had Hodgkin's paragranuloma for a period of years, later biopsies showed a transition to the granuloma. Many of the patients in this series had had proved onset of Hodgkin's disease in specific regional nodes, which were subjected to early, aggressive treatment, with successful suppression of the disease activity.

Of the 121 patients studied, 64 were males and 57 were females. Their ages ranged from 17 to 52 years, with a mean age of 32.7 years. One hundred and six of the patients had Hodgkin's granuloma by histologic diagnosis, 12 had paragranuloma, and three had sarcoma.

Correlation of the test for C-reactive protein with other laboratory determinations was not carried out in this study, but the C-reactive protein determinations were correlated with the clinical course of the patients.

Patients' Sera: Most of the 550 sera tested in the course of this study were obtained from patients in the outpatient department, but whenever a patient included in the study was hospitalized, blood samples were obtained from the wards. The evaluation of the results obtained with the sera were carried out on a "double-blind" basis. The results of the serologic tests were tabulated by patient's name, but the clinical history and status of the patient were not correlated with the results of the tests for C-reactive protein until the end of the study. This method enabled us to obtain an unbiased over-all picture of the C-reactive protein in Hodgkin's disease. Detailed information on the effect of treatment was obtained in 15 patients.

Test for C-reactive Protein: The antiserum to C-reactive protein employed in this study was obtained from rabbits injected with crystalline C-reactive protein incorporated in adjuvant. The antiserum gave no cross reactivity whatever with normal human sera.

The method used to detect the protein in serum was a capillary precipitin test employing a specific antiserum which detects C-reactive protein in concentrations as low as 0.003 mg. per cubic centimeter. The precipitin tests with antiserum were carried out in capillary tubes according to the procedure described by Anderson and McCarty.[5] This method is based on the capillary precipitin technic for serologic typing for group A streptococci described by Swift, Wilson and Lancefield.[14] C-reactive protein antiserum

(1.5 cm.) and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter). The tube was incubated at 37.5° C. for two hours and refrigerated at 4° C. overnight. Where no visible precipitate was present, the test was considered to be negative. Each millimeter of precipitate was considered 1 plus, with the maximal precipitation equal to 8 plus.

Results

Analysis of the Findings with the C-reactive Protein Test in Relation to the Classification of Hodgkin's Disease: Of the 121 patients included in this study, 35 had little or no C-reactive protein in their blood throughout the 14 months of the study. Fifteen had no C-reactive protein in their blood at the beginning of the study but became positive during the course of the study, and had large amounts of C-reactive protein consistently at the end of the 14-month period. There were 59 patients who, throughout the study,

Table 1

Summary of the Pattern of C-Reactive Protein Response of All Patients in the Three Diagnostic Categories

1. Hodgkin's sarcoma (3 patients)	Consistently positive
2. Hodgkin's granuloma	
35 patients	Consistently negative
12 patients	Changed from negative to positive
59 patients	Consistently positive
3. Hodgkin's paragranuloma	
8 patients	Consistently negative
4 patients (with generalized disease)	Consistently positive

had large amounts of C-reactive protein in their blood. The 12 patients who had Hodgkin's paragranuloma will be treated as a separate group. The pattern of C-reactive protein of all patients in the three diagnostic groups is summarized in table 1.

Hodgkin's Paragranuloma: Twelve of the patients studied had Hodgkin's paragranuloma by histologic diagnosis. Eight of these 12 were asymptomatic and remained well following treatment of the paragranuloma at the time of histologic diagnosis. The other four patients with Hodgkin's paragranuloma were symptomatic, and the character of their disease process had changed from paragranuloma to granuloma. The patients with Hodgkin's paragranuloma did not exhibit C-reactive protein in their blood until the disease became generalized through change in the character of the disease process. Table 2 shows the findings with the test for C-reactive protein in the eight patients with Hodgkin's paragranuloma who showed no clinical evidence of generalization or extension of the disease process.

The results of the test for C-reactive protein in four patients with Hodgkin's paragranuloma by histologic diagnosis whose disease had become

TABLE 2

Results of C-Reactive Protein Determinations in Eight Patients with Hodgkin's Paragranuloma, None of Whom Presented Evidence of Generalization of the Disease

Patient	Date	C-Reactive Protein	Date of Estimated Onset	Date of Pathologic Diagnosis
C. B.	9/15/53	0	1952	1953
J. B.	7/1/54 9/14/54	0 0	1946	1948
M. G.	6/1/54	0	1950	1950
T. O.	10/8/54	0	1949	1949
H. P.	8/25/53 5/20/54	0 tr	1952	1952
D. R.	5/13/54 8/25/54	0 0	1949	1954
F. S.	4/29/54 9/16/54	0 0	1951	1951
I. W.	8/27/53 8/25/54	0 0	1948	1950

generalized are shown in table 3. From this table it is evident that when Hodgkin's paragranuloma becomes generalized and invasive, C-reactive protein appears in the blood in large amounts.

Hodgkin's Sarcoma: There were only three patients in the group of 121 studied who had the histologic diagnosis of Hodgkin's sarcoma. All three

TABLE 3

Results of C-Reactive Protein Determinations in Four Patients with Hodgkin's Paragranuloma, All Presenting Evidence of Systemic Spread

Patient	Date	C-Reactive Protein	Additional Data
E. A.	3/9/54 3/23/54	3-plus 8-plus	Onset 1949. Pathologic diagnosis, Oct., 1953. Source of nodes, cervical. X-ray given Feb., 1954. Cortisone begun 2/21/54. TEM, Oct. and Nov., 1953. Condition in Mar., 1954, poor. Metastases to spine, femur
M. G.	6/24/54 9/28/54	3-plus 6-plus	Hodgkin's disease, 9/20/42. Hodgkin's paragranuloma, 5/25/50. Present status, fair. Nodes, local
F. G.	5/13/54 8/25/54	0 7-plus	Estimated onset, May, 1953. Pathologic diagnosis, August, 1953. Present status, fair
A. K.	6/22/54 7/1/54 7/22/54 8/5/54	5-plus 4-plus 3-plus 2-plus	Estimated onset, June, 1953. Pathologic diagnosis, 6/10/54. Bilateral LL involvement, Aug. 5, 1954. Treated with TEM, with good subjective improvement. Nodes, general. Spleen, 3 plus. Liver, 3 plus

had large amounts of C-reactive protein in each serum that was tested, regardless of the therapeutic regimen employed. All three had severe generalized disease with multiple systemic manifestations.

Hodgkin's Granuloma: One hundred six of the patients in the group of 121 studied had the histologic diagnosis of Hodgkin's granuloma. In many instances the diagnosis had been made when the disease was confined to regional nodes, which were subjected to early, intensive therapy. Thirty patients had been treated in this intensive way early in the course of their disease and had as yet, for varying periods of time, remained clinically well and presented no evidence of disease progression. These 30 fell into the

TABLE 4

Results of C-Reactive Protein Determinations on the Sera of Five Patients with Hodgkin's Granuloma. (The diagnoses were made while only regional nodes were involved. Treatment was given early and intensively)

Patient	Date	C-Reactive Protein	Additional Data
Ab., P.	5/27/54 8/27/54	0 0	Pathologic diagnosis, Aug., 1949. Present status, excellent. Source of nodes, left neck
Cog., J.	8/27/53 7/15/54 9/16/54	0 0 0	Estimated onset, June, 1952. Pathologic diagnosis, Dec., 1952. Present status, excellent. No metastases. Vague shadows at both lung bases. X-ray to rt. axilla, 7/1/54
Lev., S.	9/24/53 4/23/54 6/3/54 8/25/54	0 0 0 1-plus	Estimated onset, 1934. Pathologic diagnosis, 1939 (right femoral node). No metastases. No abnormal findings
Mar., V.	8/27/53 8/25/54	0 0	Estimated onset, Apr., 1948. Pathologic diagnosis (cervical node), Apr., 1951. Present status, excellent. Nodes, local. Spleen, 0. Liver, 0
Tab., L.	8/25/53 8/26/54	tr. 1-plus	Estimated onset, Jan., 1950. Pathologic diagnosis, Oct., 1951. X-ray, 6/19/53, essentially normal chest. Nodes, local. Spleen, 0. Liver, 0

group of 35 patients who, on serial bleedings, had little or no C-reactive protein in their blood. The other five patients who had little or no C-reactive protein also had Hodgkin's granuloma, but these were isolated determinations from patients on whom serial samples were unobtainable.

Table 4 presents the data obtained from serial C-reactive protein determinations on five patients with Hodgkin's granuloma who were treated intensively when early diagnosis in regional nodes was established. All five were doing well clinically, and had presented no findings indicative of metastases in the interval since the pathologic diagnosis was made and intensive treatment was given. It is evident from the table that these patients had no significant amount of C-reactive protein in their blood. The finding of small amounts of C-reactive protein in the sera of two of these patients could not be accounted for on the basis of physical findings.

The remaining 59 patients with Hodgkin's granuloma consistently had large amounts of C-reactive protein in the blood. There was an intermediate group of 12 patients with Hodgkin's granuloma who had negative tests for C-reactive protein at the beginning of the study, but by the end of the 14-month period had consistently positive determinations for C-reactive protein. There was definite clinical evidence of generalization of the disease process in nine of these 12, but the remaining three did not show definite clinical evidence of generalization at the time the study was terminated.

The 59 patients with consistently positive tests for C-reactive protein had unequivocal generalized Hodgkin's disease. Eighteen of them died during the course of this study. Table 5 shows the results of the tests for C-reactive protein on serial bleedings from one of the patients characteristic for this group.

TABLE 5

Results of C-Reactive Protein Determinations on Serial Bleedings from a Patient with Generalized Hodgkin's Disease (Granuloma), B. Lob., female, age 24

Date	C-Reactive Protein	Additional Data
3/9/54	5-plus	Hodgkin's granuloma. Onset, Mar., 1951. Pathologic diagnosis, Mar., 1951. Metastases, scapula and ischium. Condition, poor
3/16/54	8-plus	6/18/54, fever, bone pain, anemia, jaundice
3/23/54	6-plus	Nodes, local. Spleen, 2 plus. Liver, 0
3/30/54	6-plus	X-ray, Jan., 1953; Oct., 1953
4/16/54	5-plus	Cortisone, 1953
4/20/54	6-plus	
5/11/54	6-plus	
6/8/54	6-plus	
7/6/54	6-plus	

Effect of Treatment on C-reactive Protein in Patients with Generalized Hodgkin's Disease: Fifteen patients with generalized Hodgkin's disease who had large amounts of C-reactive protein appearing in their sera were bled weekly or bi-weekly for periods of two and three months before, during and following treatment with agents currently used for therapy of Hodgkin's disease. Illustrative records of the treatment and course of two of these patients are present in tables 6 and 7. The first of these patients (M. I., a 37 year old male), was given a course of radiation therapy which was followed by marked clinical improvement. As is evident from examination of table 6, the C-reactive protein did not disappear from the blood during or following the course of radiation therapy, although there was some diminution in the C-reactive protein, as evidenced by the semiquantitative precipitin test. This was similar to the findings in six other patients of this group who were treated with x-ray. In none of these did the C-reactive protein disappear completely from the blood in response to courses of radiation, although satisfactory clinical improvement ensued. Similar results were obtained with nitrogen mustard and adrenocortical hormone therapy.

The findings in patient R. V., a 29 year old female who was treated with

large doses of prednisone and with ACTH gel, are detailed in table 7. It appears evident that, once extensive generalization of Hodgkin's disease has occurred, intensive therapy of any kind does not cause the disappearance of the C-reactive protein from the blood.

TABLE 6

Results of Serial Determinations for C-Reactive Protein on the Serum of a Patient with Generalized Hodgkin's Disease (Granuloma) Treated with Radiation, M. I., male, age 37

Date	C-Reactive Protein	ESR, mm./hr.	Max. daily temp., °F.	Rx	Clinical Status
11/29/55	5+	115	100.6	None	Fever, low back pain. No glandular enlargement
12/5/55	4+		99.6	None	Back pain, nodule (Hod.) in RLL
12/7/55	4+		99.6	None	
12/9/55	4+		98.6	None	Pain, subsided
12/12/55	6+		98.6	None	
12/13/55	3+		98.2	None	Asymptomatic
12/16/55	2+		98.4	None	Asymptomatic
12/30/55	4+	115	102.2	Rad. Rx to mediastinum, lungs and dorsal spine	Chest and back pain
1/3/56	4+		100	Rad. Rx to mediastinum, lungs and dorsal spine	Enlarged left iliac nodes, rt. axillary nodes
1/9/56	3+		99.8	Rad. Rx to mediastinum, lungs and dorsal spine	Anorexia, weight loss, weakness
1/10/56	1+	122	100.2	Rad. Rx to mediastinum, lungs and dorsal spine	
1/16/56	3+	136	102.4	Rad. Rx to mediastinum, lungs and dorsal spine	
1/17/56	1+		102	Rad. Rx to mediastinum, lungs and dorsal spine	Infiltration demonstrated in left kidney by intravenous pyelogram
1/18/56	1+		101.4	Rad. Rx to mediastinum, lungs and dorsal spine	
1/20/56	2+		102	CB 1348 (1/24)	Oral phenol mustard (B-W)
1/27/56	tr.		99	CB 1348 (1/24)	
2/8/56	2+		99.8		Feels well, adenopathy diminished
2/17/56					Gaining weight. Temperature below 100°

TABLE 7

Results of Serial Determinations for C-Reactive Protein on the Serum of a Patient with Generalized Hodgkin's Disease (Granuloma) Treated with Prednisone and ACTH Gel, R. V., female, age 29

Date	C-Reactive Protein	ESR, mm./hr.	Max. daily temp., °F.	Rx	Clinical Status
8/12/55	4+		101.8	Prednisone 60 mg.; ACTH gel, 25 u.	Spiking temperature, epigastric mass
8/15/55	4+		102	Same—2 units blood	Spiking temperature unchanged
8/18/55	5+		102.6	Prednisone, 80 mg.; ACTH gel, 25 u.	
8/19/55	4+	60	101.2	Prednisone, 90 mg.	
8/24/55	5+		102.4	Prednisone, 100 mg.; ACTH, 50 u. IV; ASA, 2.4	Condition improved
8/26/55	4+		101	Prednisone, 100 mg.; ACTH, 50 u. IV; ASA, 2.4	No change
8/29/55	8+		102	Prednisone, 100 mg.; ACTH, 50 u. IV; ASA, 2.4	No change
8/30/55	3+		102.2	Prednisone, 100 mg.; ACTH, 50 u. IV; ASA, 2.4	Monilia in mouth. Dullness and diminished BS, both bases
9/2/55	5+		102.4	1 unit blood	No change
9/6/55	4+		101.4	Prednisone, 35 mg.; ACTH, 50 u.	Epigastric distress. Pulmonary edema
9/12/55	5+		99.6	Prednisone, 100 mg.; Digoxin	Monilia gone. Temperature going down. Doing better. Eating
9/15/55	5+		100	Prednisone, 100 mg.; Digoxin	Sitting up. Cheerful
9/21/55	6+		102	Prednisone; Digoxin; Trans. ×3.	Bloody diarrhea. Anemia of 6.0 gm.%
9/27/55	5+		102.2	Prednisone, 75 mg.; ACTH, 25 u.	Petechiae, spiking temperature, enlarging epigastric mass
9/28/55	6+		101	None	Weak, anemic
10/4/55					Deceased

Regularity of the Presence of C-reactive Protein in Generalized Hodgkin's Disease: In this series all of the patients who by clinical criteria had generalization of their disease process had significant amounts of C-reactive protein in their blood. Only a few of those who were considered not to have

clinical activity of their Hodgkin's disease had C-reactive protein in their serum. This finding appears to indicate that the C-reactive protein is present with great regularity in the sera of patients with active, metastasizing Hodgkin's disease. These findings are most clearly illustrated by the group of 12 patients with paragranuloma by histologic diagnosis. The eight patients with paragranuloma who showed no clinical evidence of disease activity did not have C-reactive protein in their sera. The four patients whose paragranuloma had become infiltrative and generalized had large amounts of this abnormal protein in their blood. In this series of patients there were too few whose serial determinations for C-reactive protein turned positive during the course of the investigation to determine whether the appearance and persistence of the C-reactive protein in the serum of patients with Hodgkin's disease can be taken as a reliable signal of reactivation and generalization of the disease process, but in the light of the findings on all the patients included in the study it seems probable that the appearance or reappearance of C-reactive protein in the blood may indicate a change in the character of the disease.

Once generalization of the disease process has occurred, different forms of treatment appear to have no consistent, reliable effect in causing the disappearance of C-reactive protein from the blood. This finding is in marked contrast to the extensive experience in the field of rheumatic fever, where adequate treatment of the patient with salicylates or steroid hormones causes the C-reactive protein to disappear promptly from the blood.

Discussion

C-reactive protein, an abnormal substance associated with conditions characterized by tissue damage and inflammation, has previously been described as occurring in patients with Hodgkin's disease and other neoplasms, particularly those with metastases. It is of interest in this connection to note that the sera of patients with metastatic carcinoma often contain large amounts of C-reactive protein, whereas in the earlier stages of the malignancy, as in the case of carcinoma of the breast, C-reactive protein may be absent from the blood.[12] The data obtained in this study indicate that C-reactive protein is present in the blood of patients with generalized Hodgkin's disease consistently and in large amount. Whether the presence of the C-reactive protein in the sera of these patients is an indicator specifically of Hodgkin's disease activity or whether it is a measure of tissue destruction and infiltration cannot be said.

From the findings obtained in patients treated by a variety of methods, it seems evident that the test for the presence of C-reactive protein in the sera of patients with Hodgkin's disease cannot be used as an index of successful treatment. Intensive therapy of 15 patients with severe generalized Hodgkin's disease did not in any instance result in complete disappearance of the C-reactive protein from the blood, despite apparent clinical improve-

ment. This is in contrast to the findings obtained in all infectious diseases successfully treated with antibiotics, and in the instance of rheumatic fever, where suppression of rheumatic activity by adequate salicylate or hormone therapy causes prompt disappearance of the C-reactive protein from the blood. This difference suggests that the C-reactive protein may be present in the blood of patients with Hodgkin's disease due to causes other than inflammation—perhaps to invasion of tissue.

Although the C-reactive protein has been widely studied in a variety of disease conditions during the past five years, nothing is as yet known as to the site of its origin or its possible function in the vast array of diseases and injuries in which it is present. Since this abnormal protein appears in the blood in such diverse conditions as pneumococcal pneumonia, rheumatic fever, malaria, Hodgkin's disease, fractures and other injuries, the protein may be elaborated by a cellular system such as the reticuloendothelial system, which is involved in the primary host response to infection and injury.

Summary and Conclusions

Serial determinations for C-reactive protein, carried out on sera from 121 patients with Hodgkin's disease, showed:

1. A change in Hodgkin's paragranuloma to a disseminated form of Hodgkin's disease is mirrored in the appearance of C-reactive protein in the blood.
2. Following early, aggressive treatment of localized Hodgkin's granuloma, C-reactive protein disappears from the blood. With recrudescence of disease activity, the C-reactive protein reappears and, with generalization of the disease, persists.
3. C-reactive protein does not provide an accurate, sensitive measure of response to therapeutic agents in patients with generalized Hodgkin's disease.
4. In patients with generalized Hodgkin's disease there is no consistent effect on C-reactive protein by the various therapeutic agents, despite clinical improvement.

Summario in Interlingua

Proteina C-reactive es un anormal proteina seral que occurre in le sanguine de patientes con varie disordines. Illo ha essite studiate le plus intensemente in patientes con morbos infectiose e con febre rheumatic, sed il existe plure reportos de investigationes in grande numeros de individuos non-seligite. Le presente studio se occupa de proteina C-reactive in patientes con morbo de Hodgkin. Determinationes in serie del proteina C-reactive esseva effectuate con le seros de 121 patientes con le morbo mentionate. Le determinationes esseva effectuate per medio de un antisero specific pro proteina C-reactive. Iste antisero monstrava nulle reactivitate cruciate del toto con normal sero human. Esseva constatate que le transition ab paragranuloma de Hodgkin a un forma disseminate de morbo de Hodgkin es reflectite in le apparition

de proteina C-reactive in le sanguine de patientes qui previemente non habeva iste proteina anormal. Post le precoce e aggressive tractamento de localisate granuloma de Hodgkin, le proteina C-reactive dispare ab le sanguine del patiente. Quando il occurre un recrudescentia del activitate del morbo, il etiam occurre le re-apparition del proteina C-reactive, e quando le morbo deveni generalisate, le proteina C-reactive persiste in le sanguine. In omne le casos studiate, patientes con sever granuloma generalisate de Hodgkin habeva grande quantitates de proteina C-reactive in lor sanguine. Esseva trovate que variationes in le quantitate del proteina C-reactive in le sanguine del patientes non representava un accurate e sensibile mesura del responsa del patientes al agentes therapeutic usate in le tractamento de morbo generalisate de Hodgkin. In plus, in patientes con generalisate morbo de Hodgkin, il non esseva possibile constatar un effecto systematic exercite super le proteina C-reactive per le varie agentes therapeutic nunc disponibile, sin reguardo a si o non illos produceva un melioration del stato clinic del patiente.

BIBLIOGRAPHY

1. Tillett, W. S., and Francis, T., Jr.: Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus, J. Exper. Med. **52**: 561, 1930.
2. Ash, R.: Non-specific precipitins for pneumococci fraction C in acute infections, J. Infect. Dis. **53**: 89, 1933.
3. Roantree, R. J., and Rantz, L. A.: Clinical experience with the C-reactive protein test, Arch. Int. Med. **96**: 674, 1955.
4. Sprunt, D. H., Hale, W. M., Chang, F. C., Richmond, S. G., and Erikson, C. C.: Present status of cancer tests, Science **122**: 273–274, 1955.
5. Anderson, H. C., and McCarty, M.: Determination of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever, Am. J. Med. **8**: 445, 1950.
6. Ziegra, S. R., and Kuttner, A. G.: Re-appearance of abnormal laboratory findings in rheumatic patients following withdrawal of ACTH or cortisone, Am. J. M. Sc. **222**: 516, 1951.
7. Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive protein in serum as a guide to the treatment and management of rheumatic fever, Am. J. Med. **15**: 645, 1953.
8. American Heart Association: Report of the Committee on Standards and Criteria for Programs of Care of the Council on Rheumatic Fever: Jones criteria (modified) for guidance in the diagnosis of rheumatic fever, Mod. Concepts Cardiovas. Dis. **24**: 291, 1955.
9. Levinger, E. L., Levy, H., and Elster, S. K.: Study of C-reactive protein in the sera of patients with acute myocardial infarction, Ann. Int. Med. **46**: 68, 1957.
10. Kroop, I. G., and Shackman, N. H.: The C-reactive protein determination as an index of myocardial necrosis in coronary artery disease, Am. J. Med. **22**: 90, 1957.
11. Wood, H. F., McCarty, M., and Slater, R. J.: The occurrence during acute infections of a protein not normally present in the blood. V. Physical chemical properties of the C-reactive protein crystallized by a modified technique, J. Exper. Med. **100**: 71, 1954.
12. Good, R. A., and Wood, H. F.: Unpublished observations.
13. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's disease and allied disorders, 1947, Oxford University Press, New York.
14. Swift, H. F., Wilson, A. T., and Lancefield, R. C.: Typing group A streptococci by M precipitation reaction in capillary pipettes, J. Exper. Med. **78**: 127, 1943.
15. Lewis, A. J., Pader, E., and Elster, S. K.: The effect of salicylate and adrenocortical hormones on C-reactive protein, Am. J. M. Sc. **233**: 309, 1957.

THE EARLY DIAGNOSIS OF RUPTURED ABDOMINAL ANEURYSM *

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Sudden rupture of a saccular aneurysm of the abdominal aorta is no longer a necessarily fatal condition. Successful resection of ruptured aneurysms has been reported, although the number of survivals is still small.[1, 2] Accurate, early diagnosis can markedly reduce both the immediate mortality and the late deaths, which are principally due to distal tubular necrosis. This report deals with three diagnostic aids which have not been sufficiently stressed but are frequently helpful in arriving at an early diagnosis. These aids consist of ecchymosis in the lower abdomen or perineum,[3] loss of deep tendon reflexes in the lower extremities,[4] and loss of the psoas shadows in abdominal roentgenograms.[5, 6]

During the last five years 18 patients with ruptured abdominal aneurysms have been admitted to the Albany Hospital, but in only seven was the diagnosis made in time to permit surgical exploration. Each case presented as an acute abdominal catastrophe, the nature of which was often confused with a variety of other conditions, particularly perforated peptic ulcer, ureteral calculus, volvulus of the sigmoid colon, acute pancreatitis and perinephric abscess. The variety of clinical signs and symptoms seen in ruptured abdominal aortic aneurysms suggests that their diagnosis should be suspected in any elderly patient with unexplained sudden abdominal or back pain. This is especially true if the sudden pain is accompanied by a history of gnawing pain, often suggestive of renal disease, a previously noted pulsatile mass or roentgen evidence of calcification in the region of the aorta. At the time of rupture there may be clinical signs of shock, peritoneal irritation and abdominal distention. A bruit may be heard in the abdomen or over the femoral arteries. The presence of these signs will depend, in general, on whether the retroperitoneal hematoma has broken into the free peritoneal cavity, which will permit more rapid blood loss and lead to a chemical peritonitis. The diagnostic clues we wish to emphasize in this report are found in the period immediately following rupture, when the blood loss is still confined to the retroperitoneal space and before peripheral collapse and peritonitis have developed.

Ecchymosis of the lower abdominal wall or perineum results from dissection of the retroperitoneal blood along the surface of the psoas muscle

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to its exit from the abdomen. In two cases of the present series where ecchymosis was observed, the history was of five and seven days' duration, respectively, giving ample time for the blood to reach the surface of the body.

Neurologic findings have been frequently noted in patients with dissecting aneurysms, and are thought to be due to narrowing of the orifices of the spinal arteries. It has not been sufficiently stressed that a large retroperitoneal hematoma may extend behind the aorta for a considerable distance and compress the spinal arteries with a similar result. Three of our cases

FIG. 1. *Case 2.* Roentgenogram demonstrating loss of left psoas shadow.

showed a loss of deep tendon reflexes on one or both sides. Case 1 was admitted to the hospital with a diagnosis of ruptured intervertebral disc because of the neurologic findings of a foot drop and loss of knee and ankle jerks.

A large retroperitoneal hematoma will frequently obscure the psoas shadow on a plain abdominal roentgenogram (figure 1). This latter finding has been the most useful clue where the diagnosis has been in doubt. "Widened psoas shadow suggestive of psoas abscess or tumor" was first reported in 1934 by Held and Goldbloom.[5] Rusche and Bacon in 1935 [6] surgically explored an elderly man with the diagnosis of psoas abscess, based

on obliteration of the psoas shadow, only to discover a ruptured aneurysm. Lipshutz and Chodoff [7] have called attention to calcification and displacement of the aorta as well as obliteration of the psoas shadow. In spite of these reports this diagnostic tool has not been widely employed in patients with unexplained abdominal pain. Five of our six patients in whom roentgenograms were obtained demonstrated loss of the psoas shadow. In three of these cases the correct diagnosis was made only after a plain film had been taken.

The following three illustrative case reports indicate the variability of the clinical picture of ruptured abdominal aortic aneurysm and emphasize the value of the diagnostic measures discussed above.

Case Reports

Case 1. A 77 year old widowed white female was admitted on July 30, 1955, with the chief complaint of lower abdominal pain for five days. She was uncoöperative and refused to answer questions fully, but the information was obtained that she had been well until five days prior to admission, when lower abdominal pains had begun, associated with vomiting on one occasion and constipation for two days.

Past History and Family History: Not obtainable.

Physical Examination: Blood pressure, 190/110 mm. of Hg; pulse, 80; respirations, 20; temperature, 97° F. The patient was an obese, elderly, irascible female who would not permit a complete physical examination.

Positive Findings: The lungs were clear. The heart was regular; it was enlarged, and there was an aortic systolic murmur. The abdomen was symmetric and tender. The liver was palpable two fingerbreadths below the right costal margin. *There were ecchymotic areas over the lower abdomen.*

Laboratory Findings: Hemoglobin, 14 gm.; hematocrit, 46%; white blood count, 8,800. Blood sugar, 140 mg.%. Nonprotein nitrogen, 25 mg.%. Amylase, 126 units. Prothrombin time, 18 sec., 50%.

Course: The patient was placed on bed-rest and analgesia. She persistently refused further examination. The day following admission she was found walking from the hospital. She stated she was dying, and died on being returned to her bed. Postmortem examination revealed a ruptured arteriosclerotic aortic aneurysm.

Case 2. This 60 year old white male had a total of three hospital admissions of interest here. He was first admitted to the Albany Hospital in November, 1955, with complaint of crampy pain in the posterior aspect of both thighs, more pronounced on the right, deep and aching in nature and often waking him at night. This responded temporarily to heat, massage and calcium. Physical examination revealed a moderately obese elderly white male in no distress. Positive findings were good peripheral pulses, and a limping gait with slight right foot drop and weakness and atrophy of the right gastrocnemius. The right ankle jerk was absent. The impression at that time was that the patient had a herniated disc at L4–L5, or L5–S1 on the right. After refusing further study he was discharged to receive physiotherapy.

Second Admission: The patient was re-admitted in January, 1956. He had been fairly well since the day of discharge until he experienced a pain like a sudden, severe, "sledge-hammer" blow in his abdomen and thighs. He became ashen, cold and perspiring, and lost consciousness on the way to the emergency room. Physical examination revealed an acutely ill, cold, perspiring, cyanotic adult white male. Blood pressure, 110/90 mm. of Hg; pulse, 88; respirations, 20. The abdomen was protuberant and painful to palpation, and there was a nonpulsating mass in the

epigastric region. Femoral pulses were palpable, the dorsalis pedis pulses absent. Knee jerks and ankle jerks were absent bilaterally.

A portable plain film of the abdomen revealed absence of the psoas shadow. Operation was performed and a ruptured aortic aneurysm of the abdominal aorta was resected and replaced by a vinyon graft. The patient received 21 transfusions preoperatively and postoperatively. He was discharged improved in February with stay sutures in place.

Third Admission (February, 1956): On the fourth day following his discharge the patient suddenly developed acute abdominal pain, vomited, and had no detectable blood pressure when brought to the emergency room. Administration of Levophed raised the blood pressure to 104/60 mm. of Hg, but the patient remained in poor condition, with a protuberant, tender and rigid abdomen. Superficial infection was noted in the abdominal wound. The patient was transfused when his hematocrit fell from 37% on admission to 28%. He died during the course of laparotomy and was found to have a leak in the graft, apparently caused by infection at that site.

Case 3. A 63 year old Chinese male was brought to the emergency room on April 10, 1956, with the chief complaints of weakness and vomiting. He had been treated for three to four years for hypertension with Thorazine and Serpasil by his physician. One week prior to admission, back pain had developed which persisted for one week, then became much worse on the day prior to admission; at midnight the patient vomited and fainted, and was brought to the emergency room in shock.

Past History revealed that he had been treated for syphilis in 1940.

Physical Examination demonstrated an elderly, acutely ill Chinese male. Blood pressure, 96/62 mm. of Hg; pulse, 80. Positive findings were distant heart tones, and a large pulsatile abdominal mass, approximately at the umbilicus. No bruit was heard.

Laboratory Findings: Hematocrit, 37%; nonprotein nitrogen, 45 mg.%. Serologic test for syphilis was negative. A plain film of the abdomen revealed that the left psoas shadow was obliterated. An electrocardiogram was within normal limits.

Hospital Course: The patient was taken to the operating room, received multiple transfusions and a saccular, arteriosclerotic aneurysm of the abdominal aorta was resected and a vinyon graft inserted. Patient required reëxploration for hemoperitoneum, which was attributed to generalized ooze. His postoperative course was one of gradual improvement. He was discharged on May 11, 1956, to a nursing home, which he has since left. On his last ambulatory visit to the clinic his femoral pulses were noted to be bounding.

Summary

Three cases of ruptured arteriosclerotic aneurysm of the abdominal aorta are presented to illustrate the features which made early diagnosis and surgery possible in seven of 18 such patients admitted to the Albany Hospital in the last five years. Roentgenograms of the abdomen taken in five cases were of great diagnostic value in that the retroperitoneal hematoma obliterated the psoas and renal shadows on the side of hemorrhage. Two other diagnostic aids were observed: (1) the loss of the deep tendon reflexes of the lower extremities, common in dissecting aneurysms but rare in saccular abdominal aneurysms; (2) the presence of ecchymosis on the lower anterior abdominal wall. These findings are thought to be due to the presence of a large retroperitoneal hematoma, and may point to the correct diagnosis before rupture into the free peritoneal cavity, with its resultant

massive blood loss and peritonitis. Early diagnosis will permit utilization of the remarkable improvements of vascular surgery and lead to a markedly decreased mortality in this disease. Six of the cases presented here were operated on, with success in four cases and temporary success in two cases. The seventh patient died in the course of the operation.

SUMMARIO IN INTERLINGUA

Le ruptura subitanee de un aneurysma saccular del aorta abdominal ha cessate esser un condition a exito necessarimente mortal. Resectiones a bon successo ha essite reportate in casos de aneurysma rupturate, ben que le numero del superviventes es ancora basse. Exacte e prompte diagnoses es capace a effectuar un reduction marcate del mortalitate immediate e etiam del mortes tardive que resulta principalmente de distal necrose tubular. Le presente reporto es concernite con tres adjutas diagnostic que non es sufficientemente notate ben que illos es frequentemente utile in establir le diagnose a un tempore precoce. Illos es (1) ecchymosis in le abdomine inferior o le perineo, (2) perdita de un o plures del reflexos de tendine profunde in le extremitates inferior (commun in aneurysmas dissecante sed rar in aneurysmas abdominal saccular), e (3) perdita del umbras de psoas in roentgenogrammas abdominal.

Es presentate tres casos de rupturate aneurysma arteriosclerotic del aorta abdominal con le objectivo de illustrar le aspectos que rendeva possibile un diagnose precoce e un prompte intervention chirurgic in septe del 18 patientes qui esseva admittite con iste condition al Hospital Albany in le curso del passate cinque annos. In quatro del septe patientes le operation esseva successose; in duo alteres, illo esseva temporarimente successose; in le septime caso, le patiente moriva in le curso del operation.

BIBLIOGRAPHY

1. Cooley, D. A., and DeBakey, M. E.: Ruptured aneurysms of the abdominal aorta: excision and homograft replacement, Postgrad. Med. **16**: 334, 1954.
2. Javid, H., Dye, W. S., Grove, W. J., and Julian, O. C.: The resection of ruptured aneurysms of the abdominal aorta, Ann. Surg. **142**: 613, 1955.
3. Green, R., and Saphir, O.: Ecchymosis of the abdominal wall as an early diagnostic sign of dissecting aneurysm of the aorta, Am. J. M. Sc. **216**: 24, 1948.
4. Moersch, F. P., and Sayre, G. P.: The neurologic manifestations associated with dissecting aneurysm of the aorta, J. A. M. A. **144**: 1141, 1950.
5. Held, I., and Goldbloom, A. A.: Three rare intra-abdominal cases, S. Clin. North America **14**: 389, 1934.
6. Rusche, C. F., and Bacon, S. K.: Ruptured abdominal aortic aneurysm simulating perinephritic abscess, Brit. J. Urol. **7**: 330, 1935.
7. Lipshutz, B., and Chodoff, R.: Diagnosis of ruptured abdominal aortic aneurysm, Arch. Surg. **39**: 171, 1939.

INTRA-ARTERIAL NITROGEN MUSTARD IN THE TREATMENT OF PELVIC CANCER*†

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In advanced and nonresectable neoplastic disease certain chemical agents have been found to have some effect in slowing the growth or in producing temporary regression of the tumor tissue. Nearly all of the agents which are capable of producing such effects, when administered systemically, also have toxic effects on the bone marrow, liver or other organs. Host toxicity is the limiting factor in dosage, and prevents the use of sufficient amounts of drug to produce drastic effects on the tumor.

Klopp et al.[1-4] reported that in patients with inoperable cancer in whom the principal manifestations of the disease were largely localized to a single area, instillation of nitrogen mustard into the regional arterial blood supply produced local effects which were greater than those produced by similar doses injected systemically. When given in repeated small doses intra-arterially, a larger total amount could be safely administered than could be given by the intravenous route. Their therapeutic results were encouraging. Cromer et al.[4] found more benefit in pelvic tumors treated by the intra-arterial route than would have been expected from intravenous administration. Bierman et al.[5,6] also considered intra-arterial nitrogen mustard a practical adjunct to other types of therapy in far-advanced cancer. Subsequent reports by Bonner et al.,[7] Grady et al.[8] and Boiman et al.[9] have concluded that, in spite of evidence of therapeutic responses in some cases, the procedures employed were too time-consuming or hazardous to be considered of significant value. Review of their papers indicates that the complications encountered were of a technical nature, related to the type of procedure or the dosage schedules used. However, some therapeutic responses were obtained, and it therefore seemed likely that the palliative use of intra-arterial nitrogen mustard would be justified if a simplified, safe method were available.

Sullivan et al.[10] described a simplified method of performing these procedures using arterial catheterization via a percutaneous needle puncture.

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TABLE 1

Criteria of Evaluation

	Number of Cases	Responded	Failed
Objective			
Tumor mass	18	9	9
Oliguria	5	3	2
Obstructive edema	4	1	3
Intestinal obstruction	5	3	2
Vaginal bleeding	2	1	1
Urinary frequency	1	1	0
Ascites	1	0	1
Monoplegia	1	1	0
Fever	1	1	0
Hydronephrosis	1	1	0
	39	21	18
Subjective			
Pain	12	9	3

TABLE 2

Carcinoma of Cervix

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
1	84	18	Radium, x-ray	Pelvis	Anuria	0		—	Died 10 days after treatment of uremia
2	49	21	Radium, explor. lap.	Pelvis	Abdominal mass	+		1 month	Died 2 months after treatment of intestinal obstruction
3	40	36	X-ray, hysterectomy	Pelvis and abdomen (liver)	Vaginal bleeding	0		—	Died 1 month after treatment of vaginal bleeding and liver failure
4	44	18	Salpingo-oophorectomy, x-ray	Pelvis	Pain		+	6 weeks	Died 6 months after treatment of uremia
5	68	24	X-ray	Pelvis	Oliguria	+		3 weeks	
	68	24	X-ray	Pelvis	Oliguria	0		—	Died 2 weeks after second treatment
6	58		X-ray	Pelvis	Oliguria	+		6 weeks	Died 2 months after treatment of uremia

Their results in treating brain and head tumors appeared to demonstrate conclusively that high local concentrations of nitrogen mustard (methyl-*bis* (β-chloroethyl)-amine) or triethylene melamine could be achieved without excessive systemic effects. Eight of their 14 reported cases were treated for pelvic and/or intra-abdominal disease, with beneficial results in four of

TABLE 3

Carcinoma of Ovary

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
7	57	12	X-ray, TEM	Pelvis, abdomen	Abdominal mass Obstructive edema	+ +		More than 5 months	Died 11 months after treatment
8	40	20	X-ray	Pelvis	Abdominal mass Urinary frequency	+ +		More than 2 months	Died 4 months after treatment of pulmonary metastases
9	44	17	Hysterectomy, x-ray	Pelvis, bone metastases	Abdominal mass Obstructive edema	0 0		—	Died 2 weeks after treatment of renal failure
10	38	3	None	Pelvis, lungs	Abdominal mass Vaginal bleeding	+ +		2 months	No follow-up after 2 months
11	63	?18	None	Pelvis, lungs, liver	Oliguria	+		1 week	Died 1 week after treatment of uremia
12	29	11	Oophorectomy, x-ray	Pelvis, abdomen	Abdominal mass Ascites Obstructive edema	0 0 0		—	Died 3 weeks after treatment of cerebral metastases
13	35		Oophorectomy, x-ray	Pelvis	Abdominal mass Intestinal obstruction	+ +		1 month	Died 2 months after treatment of liver failure

these. The only complications encountered were two minor and one major arterial thromboses, all occurring in patients in whom the catheter was left in place for long periods of time. They concluded that this technic was simple enough and beneficial enough to warrant its trial in certain cases of localized cancer in which other types of therapy are not feasible.

We have enlarged upon this experience, using Sullivan's technic of catheterization of the aorta via percutaneous puncture of the femoral artery.

This series deals only with the experiences in 29 cases of metastatic or nonresectable cancer in whom the principal manifestations of the disease were in the pelvis. Each patient in this series was treated with a single dose of 0.4 mg./Kg. (the routine intravenous dosage), after which the catheter was withdrawn.

TABLE 4

Neoplasms of Uterus and Fallopian Tubes

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
14 Mixed mesodermal tumor, uterus	58	5	None	Metastases to right hip, left knee	Bone pain		+	1 months	Died 5 weeks after treatment of generalized metastases
15 Leiomyosarcoma	52	12	Hysterectomy, omentectomy, TEM	Pelvis	Abdominal mass Obstructive edema	*			Died 2 weeks after attempted treatment
16 CA uterus	54	4	Hysterectomy	Pelvis, lungs	Abdominal mass Inguinal nodes	+ +		6 months	Developed rectovaginal fistula 1 month after treatment. Palliative colostomy done. Recurrent pelvic mass 6 months after treatment
17 CA fallopian tube	52	15	Salpingo-oophorectomy, x-ray	Pelvis	Abdominal mass Partial intest. obstruction	+ +		2 months	
	52	18	Salpingo-oophorectomy, x-ray	Pelvis	Recurrent mass Recurrent obstruction	+ +		1 month	Died of intest. obstruction 3 mos. after treatment
18 CA uterus	47	58	Panhysterectomy, x-ray	Lumbar spine, pelvis	Back pain Abdominal mass	0	+	2 months	No follow-up after 2 months

* Catheter could not be inserted. HN_2 not given.

MATERIALS AND METHODS

The patients were all hospitalized in the Memorial or James Ewing Hospitals. In each case there was histologic evidence of recurrent malignant neoplastic disease; the histologic diagnoses are listed in tables 2, 3, 4, 5, 6 and 7. In a few cases primary surgery had not been carried out because of demonstrated metastases or nonresectability of the lesions. Radiation therapy had previously been given to the limit of tolerance, except in a few cases in which it was given concomitantly with or immediately after intra-arterial nitrogen mustard. Thus in all of these cases there was no further conventional therapy which might be expected to be of benefit. The specific indications for this type of therapy fell into four major classes.

TABLE 5

Rectal Carcinoma

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
19 CA rectum	27	22	A-P resection, x-ray	Pelvis, perineal wound, metastases innominate bone	Pain Hydronephrosis Perineal metastases	0 0	0	—	* Died several months after treatment of disseminated carcinoma
20 CA colon	64	48	Hemicolectomy	Abdomen	Abdominal mass Intestinal obstruction	0 0		—	Died 3 weeks after treatment of electrolyte imbalance
21 CA rectum	61	60	A-P resection, x-ray	Pelvis, perineum, lungs	Pain Perineal tumor	0	0	—	Treated with intrathecal alcohol, with relief of pain
22	54	18	Resection of sigmoid, x-ray	Abdomen	Abdominal mass Intermittent obstruction	0 0		—	Continued symptomatic treatment

* Arterial catheter could not be passed on second attempt.

1. *Large pelvic tumor masses.* In 15 cases there was discomfort due to the tumor mass. Intestinal obstruction due to extrinsic pressure by a tumor mass or tumor invasion of the intestinal wall was present in three cases.

2. *Uremia* due to ureteral obstruction by tumor mass was present in four cases. In two there was acute oliguria with azotemia which was con-

TABLE 6

Lymphoma

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
23 RCS	55	16	X-ray	Pelvis, left thigh	Obstructive edema Pain	0	0	—	Died of uremia 1 month after treatment
24 HD	30	24	X-ray, HN_2	Lumbar vertebra, generalized adenopathy	Vertebral pain Fever	+ +	+	4 weeks 4 weeks	Died of disseminated herpes zoster 4 weeks after treatment
25 RCS	47	3	Explor. lap., x-ray	Osseous lesion, right hip, liver	Pain, right hip		+	6 weeks	Died of disseminated lymphoma 6 weeks after treatment
26 RCS	20	4	None	Sacrum	Right lower monoplegia Sacral pain	+*	+	6 months	Onset disseminated RCS 3 months after treatment. Died 6 months after treatment. No recurrence of sacral lesion

* Treatment with Co^{60} started after response to HN_2 was evident.

TABLE 7

Miscellaneous Neoplasms

Case	Age	Duration of Disease (months)	Previous Therapy	Extent of Disease	Indications	Response of		Duration of Response	Subsequent Course
						Objective Criteria	Subjective Criteria		
27 Osteogenic sarcoma	24	30	Hemipelvectomy, cordotomy	Amputation stump, pelvis, liver, sacrum	Sacral pain		+	2 months	
	24	33	Hemipelvectomy, cordotomy	Amputation stump, pelvis, liver, sacrum	Sacral pain		+	3 weeks	Received further x-ray therapy. Died 8 months after treatment
28 CA kidney	42	90	Nephrectomy, x-ray	Ilium, pelvis	Pain Abdominal mass	0	+	4 months	I.V. HN_2 6 months after first treatment*
29 CA kidney	60	5	Nephrectomy	Pelvis, lungs	Abdominal mass	0			Died of disease 2 weeks after treatment

* Arterial catheter could not be passed on second attempt.

sidered immediately life-endangering. In the others, kidney damage of a more chronic type was present, with progressive hydronephrosis.

3. *Severe pelvic pain* was encountered in three patients. This was usually related to osseous metastases, demonstrable radiographically.

4. *Neurologic lesions* due to compression of the spinal cord, cauda equina or sacral roots were seen in three cases.

The remaining cases were treated in this manner because of obstructive edema of the lower extremities (present in four cases), bulky perineal tumor mass (two cases) and vaginal bleeding (two cases).

TABLE 8

Complications and Side-Effects in 29 Patients

Nausea and vomiting	24
Leukopenia	11
Thrombopenia	7
Hemorrhage	0
Technical (catheter tip lost)	1

The equipment used was as described by Sullivan.[10] The basic elements were polyethylene catheters similar to those used for cardiac catheterization.* These are semiflexible and are marked at 5-cm. intervals.

After the skin has been anesthetized with procaine, a thin-walled needle (No. 18, 19 or 20 †) is introduced directly into the femoral artery, which is easily located by palpation. The spurt of arterial blood from the needle indicates that the artery has been entered. The appropriate catheter (No. 18, 19 or 20) is then threaded through the needle and passed retrograde through the femoral artery into the abdominal aorta at a level which is

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calculated to be 2 to 3 cm. above the bifurcation. In the first few such procedures the catheter was localized by a roentgenogram taken while a few cubic centimeters of Diodrast were being injected. This has not been necessary routinely, however, since introduction of the catheter to a distance of 25 cm. from the skin puncture has proved satisfactory in the average case. This distance is modified for very tall or very short patients. It has been found helpful to fill the catheter with saline and maintain it thus by closing a three-way stopcock attached to a hypodermic needle inserted into the proximal end of the catheter. This prevents reflux of blood into the catheter and clotting. When the catheter is properly positioned, the nitrogen mustard is injected through it, followed by a few cubic centimeters of saline to flush out the system.

In no instance has any difficulty been encountered in inserting the needle into the femoral artery. On three occasions it proved impossible to advance the catheter sufficiently far into the artery. This difficulty can sometimes be obviated by inserting the needle as nearly as possible parallel to the artery to facilitate the passage of the catheter. On these three occasions, however, obstruction to the passage of the catheter was encountered, and in spite of repeated attempts, including the use of the other leg, the procedure had to be abandoned. This was attributed to atherosclerotic plaques on which the catheter tip was impinging. In the other cases the catheter could be passed without difficulty.

In most cases the nitrogen mustard was administered as a single dose of 0.4 mg. per kilogram of body weight. This dose was chosen because it is the usual intravenous dose and is generally well tolerated, with only transient bone marrow depression. A lower dose is indicated in cases of sensitive lymphosarcoma, or in patients in whom previous therapy had depressed the bone marrow. However, these modifying factors were encountered in only a few patients of this series. Single-dose administration was chosen over intermittent therapy. It was felt that retreatment could be undertaken if indicated, and this has been done in two cases. It has been found most convenient to dissolve the calculated dose of HN_2 in 10 c.c. or less.

In each case a hemoglobin level and leukocyte and platelet counts were obtained prior to treatment, and two to five times weekly during the two weeks after treatment. Other physical and laboratory observations were made as necessary to evaluate the status of the patients and the antitumor effect of the nitrogen mustard.

Results

The clinical data and responses of the patients are indicated in tables 1, 2, 3, 4, 5, 6 and 7. It is considered that in 18 patients (62%) some degree of benefit was obtained. In 11 patients (38%) there was no improvement. The therapeutic response, when it occurred, varied from three weeks to six

months in duration. One patient (case 11) is classified as showing a response to therapy because of unequivocal increase in urine volume and fall in blood urea nitrogen, although the improvement lasted only one week. In a few cases, accurate interpretation of the degree of response attributable to the nitrogen mustard therapy was somewhat clouded because other forms of treatment were also used. However, in most of these a sufficient period of observation without other therapy was possible to interpret a positive response if it occurred.

Objective criteria of evaluation were employed insofar as possible. However, in some patients in whom pain was the principal indication for treatment, the patient's subjective response was considered. In 29 patients, 39 objective signs (table 1) were observed, and a positive response occurred in 21, e.g., measurable decrease in size of a tumor mass, increase in urinary flow, etc. Treatment in 12 cases with the subjective symptom pain was followed by improvement in nine. In this, as in other therapeutic studies, the patients' desire for improvement probably tends to weight the percentage of subjective responses.

In tables 2, 3, 4, 5, 6 and 7 the patients are grouped by type of disease. Analysis of these groups separately points out the disparate results obtained with different types of malignancy. While the results obtained with intra-arterial nitrogen mustard appear to be somewhat superior to those which occur with intravenous administration, there is a close parallel between the types of tumor which respond and those which do not respond to intravenous and intra-arterial nitrogen mustard. Thus, the best results are seen in the lymphomas and carcinomas of the ovary and uterus. Carcinoma of the cervix has responded less well, and in carcinoma of the rectum no positive responses have been observed.

A few illustrative cases indicate the type of response seen:

Case Reports

Case 26. A 20 year old girl was admitted with a right lower monoplegia and a large osteolytic lesion of the sacrum which, on previous biopsy elsewhere, had been found to be reticulum cell sarcoma. She had severe sacral pain. There was no evidence of metastatic disease. Nitrogen mustard, 0.4 mg. per kilogram, was administered intra-arterially. Fourteen hours later the patient had regained some muscular function of the involved lower extremity. At that time therapy was started with CO^{60} irradiation. Twenty-four hours later she could move her leg freely, and after another seven days was able to walk. She was discharged from the hospital 30 days after admission, following a 3,000 r tumor dose to the osteolytic lesion. At the time of discharge there was roentgenographic evidence of bone healing. The only residual neurologic sign was a slight persistent right foot drop. She was re-admitted three months later with widely disseminated disease, and died three months after her re-admission. At the time of her death there had been no evidence of recurrence of the sacral lesion.

Case 25. A 47 year old man was admitted with disseminated reticulum cell sarcoma. His principal complaint was of severe pain, which was found to be due to an osteolytic metastasis in the right acetabulum. X-ray therapy to the pelvis,

not including the acetabulum, had not relieved the pain. Intra-arterial administration of nitrogen mustard, 0.4 mg./Kg., resulted in nearly complete relief of pain within 24 hours. The pain did not recur, but the patient died six weeks later of widely disseminated disease.

Case 7. A 58 year old woman with advanced metastatic carcinoma of the ovary had a large lower abdominal mass and severe edema of the lower extremities, thought to be due to impairment of venous return by the mass. X-ray therapy had been given to the pelvis previously, but the radiotherapist believed that further irradiation would not help the patient. Administration of 0.4 mg./Kg. of nitrogen mustard intra-arterially resulted in marked diminution of the size of the abdominal mass and disappearance of leg edema. Five months after treatment there had been no progression of the mass or edema. The patient returned to a distant home at that time and was not seen again. She died of her disease 10 months after treatment with nitrogen mustard.

Case 13. A 38 year old woman with carcinoma of the ovary had been found at laparotomy to have extensive peritoneal and omental metastases. She was readmitted with intestinal obstruction. X-ray therapy had previously been given, and it was thought that further irradiation would be of no value. Intra-arterial administration of 0.4 mg./Kg. of HN_2 resulted in slight decrease of her abdominal mass and complete relief of the intestinal obstruction. One month later she developed jaundice, and died of liver metastases two months after treatment. There had been no recurrence of the intestinal obstruction.

Case 6. A 58 year old woman with carcinoma of the cervix was admitted with oliguria and an elevated blood urea nitrogen due to ureteral obstruction by a pelvic mass. Following intra-arterial administration of 0.2 mg./Kg. of nitrogen mustard there was a rise in urine volume and a fall in blood urea nitrogen from 125 mg.% to 35 mg.%. Her pelvic mass decreased slightly in size. Six weeks later there was again a fall in urine volume and a rise in blood urea nitrogen, and the patient died in uremia. Retreatment with HN_2 was not attempted because of thrombocytopenia, which was found to be due to bone marrow invasion with malignant cells. Surgical nephrostomy also was contraindicated by the thrombocytopenia.

Complications and Toxicity

Hematologic: In approximately one third of the cases treated there was leukopenia which occurred seven to 14 days after treatment. In none of these did the leukocyte count fall below 1,000 per mm.[3] Transient thrombocytopenia occurred in only seven cases. In case 12, a 29 year old woman with carcinoma of the ovary with widespread abdominal metastases, hepatomegaly and ascites, there was a fall in platelets to 27,000 per mm.[3] after treatment. Several days later, when the platelets had risen to 120,000, the patient developed jacksonian seizures with coma and died. Lumbar puncture revealed increased cerebrospinal fluid pressure and slightly blood-tinged fluid. This episode was attributed to cerebral metastasis. This could not be confirmed because permission for autopsy was not obtained. There were no other cases of serious or minor bleeding.

Technical: There were no instances of bleeding from the femoral artery. Moderate pressure over the site of puncture for from one to two minutes resulted in complete hemostasis in all cases.

In one case, abrupt withdrawal of the catheter *while the needle was still*

in place resulted in shearing off the distal 4 cm. of the catheter. The procedure was completed, using the femoral artery in the other leg, and then an unsuccessful attempt was made to localize the catheter tip. There was no circulatory impairment during the remainder of the patient's life. It is now our practice never to withdraw the catheter, either for repositioning or to conclude the procedure, without first withdrawing the needle through which the catheter was inserted.

Nausea and vomiting occurred in nearly all patients. It was of the same severity and duration as are commonly encountered when HN_2 is given intravenously. It has been easily controlled by sedation with barbiturates and chlorpromazine.

Discussion

The procedure described for the intra-arterial administration of nitrogen mustard is simple, and has caused no discomfort beyond the transient nausea and vomiting usually associated with the systemic administration of nitrogen mustard. No serious hazard has been encountered. In this series some degree of improvement was noted in 62%. In 48%, improvement was of significant degree and prolonged to a period of a month or more. In the patients treated in this series we have observed definite, measurable decrease in the size of tumor masses, marked decrease in pain, and relief of obstructive nephropathy and of obstructive edema. By virtue of the experimental nature of this approach, the patients treated were selected from those for whom other, conventional therapy could no longer be expected to be of any benefit, or in whom further conventional therapy was contraindicated. Thus the improvement observed represented, for the most part, improvement which could not have been expected from the further routine management of these patients. The choice of intra-arterial over intravenous administration of HN_2 depended on the localization of the principal manifestations of the disease. This mode of therapy would not be employed for the patient with generalized manifestations of disease. However, in those in whom morbidity is related chiefly to a localized primary or metastatic tumor in the pelvis, this approach appears to be of some advantage in that the maximal concentration of the chemotherapeutic agent can be achieved at the site of maximal disease. The patients in this series were all treated with HN_2. As other agents with useful antitumor effects become available it may prove worthwhile to test their effectiveness when administered by this technic. As indicated above, the standard dosage of 0.4 mg./Kg. was utilized in most of these cases. By the use of fractionated dosage it might have been possible to achieve a greater total dosage—this has been done by those who have previously attempted the intra-arterial route of injection. However, there is no evidence that protracted administration of HN_2 has given greater therapeutic effect, and in this series single dose administration has been used. Although other authors have reported the intra-arterial chemo-

therapy of tumors localized in various areas, the current series deals only with the treatment of pelvic tumors. The dosage described here would not be suitable for tumors localized in other areas, such as the head, where full dosage may cause severe ocular damage.

We conclude that this procedure has a place in the palliative treatment of patients with pelvic malignancy. It is simple and easily mastered, and there have been no serious technical or toxic complications. Thus, it appears to be a useful adjunct to the palliative care of this particular group of patients with far advanced, inoperable neoplastic disease.

Summary

1. Twenty-nine patients with pelvic cancer have been treated with intra-arterial nitrogen mustard. Some benefit was obtained in 62% of the patients treated.

2. The procedure employed is simple and has caused no serious technical or toxic complications.

3. It is concluded that the intra-arterial administration of nitrogen mustard is a useful procedure in the palliative care of patients with pelvic neoplasms of ovarian, uterine or lymphomatous origin.

Summario in Interlingua

Varie autores ha usate administrationes intra-arterial de mustarda a nitrogeno in le tractamento de canceres localisate. Certe autores considera lo como un adjuncto practic a altere typos de therapia, sed alteres opina que illo es troppo hasardose o troppo complicate. Un revista del pertinente reportos indica que le complicationes esseva le effecto del modo chirurgic usate pro attinger le arteria o etiam del programma de dosages.

In le presente serie solmente patientes con cancere del pelve es considerate. Le technica usate esseva catheterisation del aorta abdominal via le arteria femoral. Le catheter esseva inserite per medio de un punctura percutanee que esseva effectuate con un agulia a parietes tenue. In le majoritate del casos un sol dose de mustarda a nitrogeno de 0,4 mg per kg de peso corporee esseva administrate. Nulle serie complicationes esseva notate. Un certe grado de melioration occurreva in circa 60 pro cento del casos tractate. Le melior resultatos esseva observate in lymphomas e carcinomas del ovario e del utero. Le resultatos esseva minus bon in carcinoma del cervice, e nulle responsa esseva obtenite in cancere rectal.

Iste technica es considerate como utile in le tractamento palliative de patientes con malignitate pelvic. Technicamente illo es simple, e illo ha causate nulle serie complicationes.

BIBLIOGRAPHY

1. Klopp, C. T., Bateman, J. C., Berry, N., Alford, C., and Winship, T.: Fractionated regional cancer chemotherapy, Cancer Research **10**: 229, 1950.
2. Klopp, C. T., Alford, T. C., Bateman, J. C., Berry, G. N., and Winship, T.: Fractionated intra-arterial cancer chemotherapy with methyl bis amine hydrochloride: a preliminary report, Ann. Surg. **132**: 811, 1950.
3. Bateman, J. C., Klopp, C. T., and Cromer, J. K.: Hematologic effects of regional nitrogen mustard therapy, Blood **6**: 26, 1951.

4. Cromer, J. K., Bateman, J. C., Berry, G. N., Kennelly, J. M., Klopp, C. T., and Platt, L. I.: Use of intra-arterial nitrogen mustard therapy in the treatment of cervical and vaginal cancer, Am. J. Obst. and Gynec. **63**: 538, 1952.
5. Bierman, H. R., Shimkin, M. B., Byron, R. L., Jr., and Miller, E. R.: The effects of intra-arterial administration of nitrogen mustard. V. Congrès internationale du Cancer, 1950, Hermann, Paris, p. 186.
6. Bierman, H. R., Byron, R. L., Jr., and Kelly, K. H.: Therapy of inoperable visceral and regional metastases by intra-arterial catheterization in man, Cancer Research **11**: 236, 1951.
7. Bonner, C. D., Thurman, A., and Homburger, F.: A critical study of regional intra-arterial nitrogen mustard therapy in cancer, Ann. Surg. **136**: 912, 1952.
8. Grady, E. G., Krantz, S., and Brown, P. F.: Treatment of cancer by intermittent injection of nitrogen mustard via cannulated arteries, Ann. Surg. **137**: 366, 1953.
9. Boiman, R. E., Holzaepfel, J. H., and Barnes, A. C.: Intra-arterial nitrogen mustard in advanced pelvic malignancies, Am. J. Obst. and Gynec. **72**: 1319, 1956.
10. Sullivan, R. D., Jones, R., Jr., Schnabel, T. G., and Shorey, J. McC.: The treatment of human cancer with intra-arterial nitrogen mustard (methyl bis (2-chloroethyl) amine hydrochloride) utilizing a simplified catheter technique, Cancer **6**: 121, 1953.

CASE REPORTS

DYNAMIC PULMONARY REGURGITATION ASSOCIATED WITH A BICUSPID VALVE *

By JANET DICKENS, M.D., GEORGE T. RABER, B.S., and HARRY GOLDBERG, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

DYNAMICALLY significant pulmonary regurgitation of organic origin has been infrequently observed. Renewed interest in the antemortem diagnosis has been shown by several recent reports in the literature. The diagnosis was suggested from the clinical findings and/or right heart catheterization data in five such cases.[1-5] In only one of these patients,[3] however, were autopsy data available demonstrating an associated abnormal valve. In two cases [1, 2] the clinical diagnoses were gonococcal endocarditis and tetralogy of Fallot; in the two remaining cases the underlying etiology of the pulmonary insufficiency remained unknown.

The case to be reported is of interest since complete data were obtained, including right heart catheterization. The diagnosis was conclusively proved antemortem at surgical exploration, and was further supported by the finding of an abnormal bicuspid pulmonary valve at autopsy some months later.

CASE REPORT

A 46 year old white female was admitted to Hahnemann Hospital complaining of marked exertional dyspnea and ankle edema. The patient had been in apparent good health prior to an automobile accident three years previously, after which she had developed substernal pain on exertion. This was followed two to three months later by progressive exertional dyspnea. Cyanosis of the lips and nail-beds subsequently was noted on exertion, and during the following year ankle edema, abdominal swelling, a right pleural effusion and orthopnea developed. Digitalis and diuretics were used for a short time. There was no history of nocturnal dyspnea or hemoptysis. A heart murmur was first noted only a few weeks prior to admission.

On admission the patient appeared to be chronically ill. There was slight neck vein distention. The heart was enlarged, and gallop rhythm was present. A grade II harsh systolic murmur was heard at the apex and along the left sternal border, and an early, rough diastolic murmur was heard along the left sternal border. The pulmonic second sound was accentuated and split. The blood pressure was 100/80 mm. of Hg. Examination of the chest revealed decreased breath sounds and dullness to percussion at the right base. The liver was palpated seven fingerbreadths below the right costal margin, the spleen six fingerbreadths below the left costal margin.

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Ascites and pitting edema of the abdominal wall were present. One to 2 plus ankle edema and dependent cyanosis of the feet were noted.

The electrocardiogram revealed decreased amplitude of all complexes in all leads (figure 1). Chest x-rays (figure 2) revealed a right pleural effusion and moderately enlarged heart, with 2 plus enlargement of the right ventricle, pulmonary artery segment and hilar vessels. Other laboratory data were within normal limits, except for a moderately elevated blood sugar.

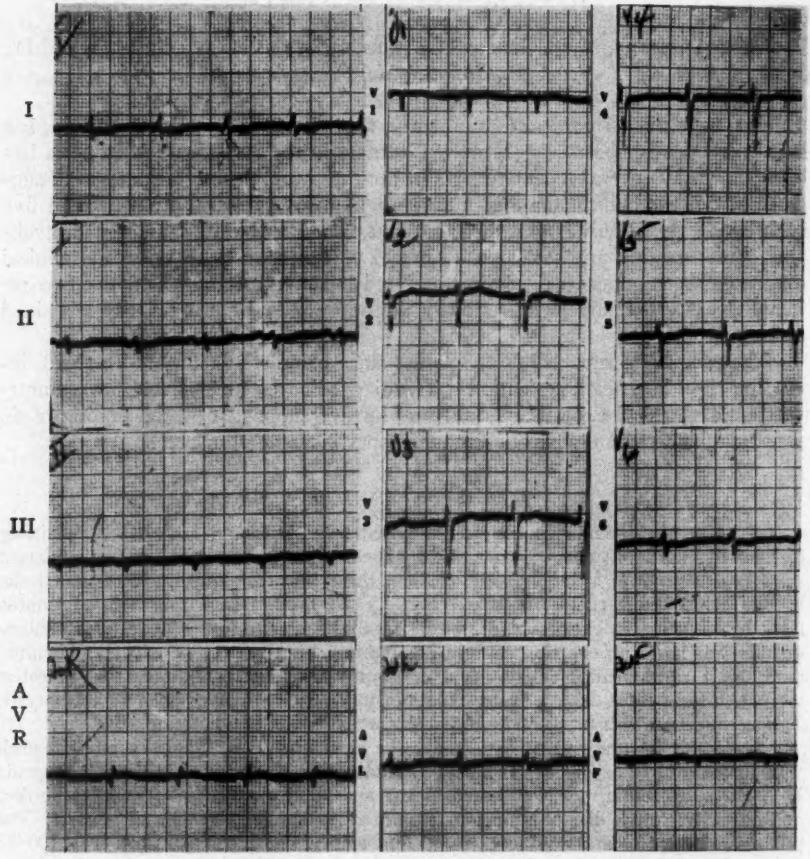

FIG. 1. Electrocardiogram showing decreased amplitude of all complexes.

Cardiac catheterization was performed. No intracardiac shunt was demonstrated. The data are shown in table 1. The contours of the pressure tracings (figure 3A) suggested a diagnosis of constrictive pericarditis.

Exploratory thoracotomy was performed on February 25, 1954. There was no evidence of constrictive pericarditis. A diastolic thrill was palpated over the enlarged pulmonary artery and right ventricle, and the pulmonic second sound was faint. On constriction of the pulmonary artery the thrill diminished and the impulse

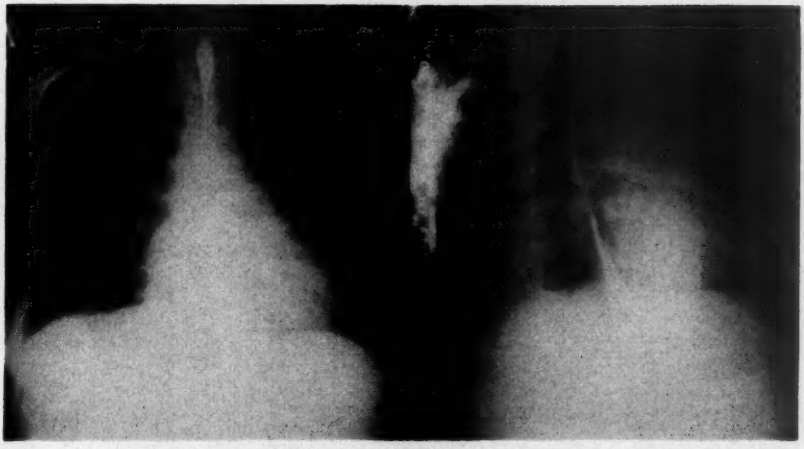

FIG. 2. Chest x-ray (posteroanterior and lateral views) after removal of right pleural effusion, showing general cardiac enlargement.

of the second sound against the examining hand increased. The pulmonary valve, examined through a stab incision in the right ventricle, was found to be insufficient. Correction was attempted by placing a nylon ribbon about the pulmonary artery close to the annulus and constricting it until the thrill was markedly diminished and the impulse of the pulmonic second sound became more prominent.

Exploration of the mitral and tricuspid valves and the auricular and ventricular septa revealed no defects. A pulmonary arteriovenous fistula and a patent ductus were also excluded by exploration.

A lung biopsy obtained at the time of surgery revealed microscopic evidence of pulmonary arteriosclerosis and arteriolosclerosis. A diagnosis of primary pulmonary hypertension with pulmonary insufficiency was made.

Despite the attempted correction of the defect the patient continued downhill and died five months following surgery.

At autopsy the heart weighed 300 gm. The right atrium was dilated, the wall measuring 0.1 cm. The right ventricular wall measured 0.3 cm. at the apex of the

TABLE 1

Cardiac Catheterization Data

	Oxygen Content (vol.%)	Pressures mm. Hg
Oxygen consumption, 271 c.c./min.		
Right atrium—high	10.2	(18)
mid	9.7	
low	6.8	
Superior vena cava	10.2	(17)
Inferior vena cava	10.7	(18)
Right ventricle—outflow	10.7	73/10
mid	9.8	
tricuspid	10.2	
Main pulmonary artery	12.0	75/25 (42)
Pulmonary venous capillary		(10)
Brachial artery	18.8 (93.5% saturated)	
Cardiac output, 3.4 L./min.		
Pulmonary arteriolar resistance, 753 dynes sec. cm.$^{-5}$		

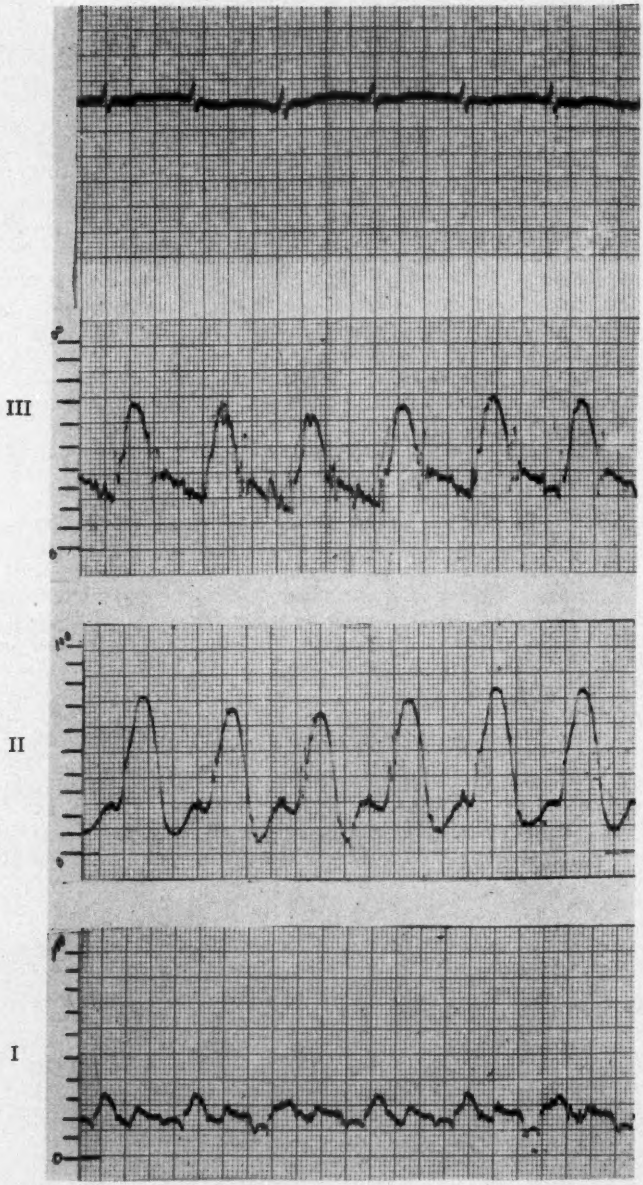

FIG. 3A. Pressure tracings obtained by right heart catheterization showing: (I) right atrial tracing, below; (II) right ventricle, middle; (III) pulmonary artery, above.

heart and 0.9 cm. at the level of the papillary muscles. The pulmonary artery measured 8.0 cm. and the pulmonary valve 7.0 cm. in circumference. The right and left posterior cusps were fused. The anterior cusp appeared to be normal. The left atrial wall and the left ventricle measured 0.2 cm. and 1.2 cm., respectively. The mitral, tricuspid and aortic valves were normal. Moderate coronary arteriosclerosis was present, with patchy areas of fibrosis throughout the myocardium and septum. Thrombotic occlusions of the right coronary artery, approximately 1.7 cm. from its origin, and the anterior descending branch of the left coronary artery in the region of the nylon suture were noted.

The bicuspid pulmonary valve was normal histologically. Severe pulmonary emphysema and moderate fibrosis were present. Pulmonary arteriolosclerosis and hyaline necrosis were observed microscopically.*

Comment: The incidental finding of a bicuspid pulmonic valve at autopsy, unaccompanied by clinical signs and symptoms related to the heart, while uncommon, has been not infrequently reported.[6, 7] In only four cases,[3, 8-10] however, has this valvular anomaly been associated with clinical signs and symptoms of right heart failure and an early diastolic murmur over the pulmonic area or along the left sternal border suggesting associated pulmonic regurgitation. The presence of congestive failure in two of these cases [8, 9] cannot be attributed solely to pulmonic insufficiency, since additional cardiac lesions were present, i.e., rheumatic involvement of the mitral and tricuspid valves in the case of Schwartz and Shelling,[8] and aortic aneurysm with aortic insufficiency in one of the cases reported by Grawitz.[9] In the case of two patients [9, 11] in whom no diastolic murmurs were heard, congestive failure could not be based upon the presence of pulmonic insufficiency, since associated aneurysms of the aortic arch in one, and bacterial endocarditis and pulmonary arterial thrombosis in the other, could alone have resulted in cardiac failure.

In only two cases,[3, 10] then, was the presence of a diastolic murmur and congestive failure unassociated with other cardiac defects. In both, chronic pulmonary disease was present—healed tuberculosis with fibrosis, and emphysema, respectively.

That pulmonary regurgitation may exist without significant alteration in cardiac dynamics has been previously suggested.[7, 10, 12] Recently, the experimental production of pulmonic insufficiency in dogs [13] failed to produce significant changes in auricular pressure or work tolerance over a period of months. Similarly, the development of a diastolic murmur following open valvuloplasty [14] was unassociated clinically with cardiac decompensation.

Nevertheless, changes in the right heart pressure tracings can be demonstrated in the presence of a significant pulmonary regurgitation, both clinically [1-5, 14] and following experimental valvulotomy.[15]

The right atrial, right ventricular and pulmonary arterial pressure tracings obtained in this case are shown in figures 3A and 3B. The right atrial curve shows a prominent "a" wave. The right ventricular systolic pressure curve is elevated and falls rapidly at the end of systole, but not to zero. Shortly thereafter there is a rapid rise to a plateau, persisting to the end of diastole.

The pressure volume relationship of this ventricle is influenced by three factors: (1) the regurgitant volume from the pulmonary artery, (2) venous inflow

* Autopsy was performed by Edwin H. Ziegler, M. D., St. Joseph's Hospital, Lancaster, Pennsylvania.

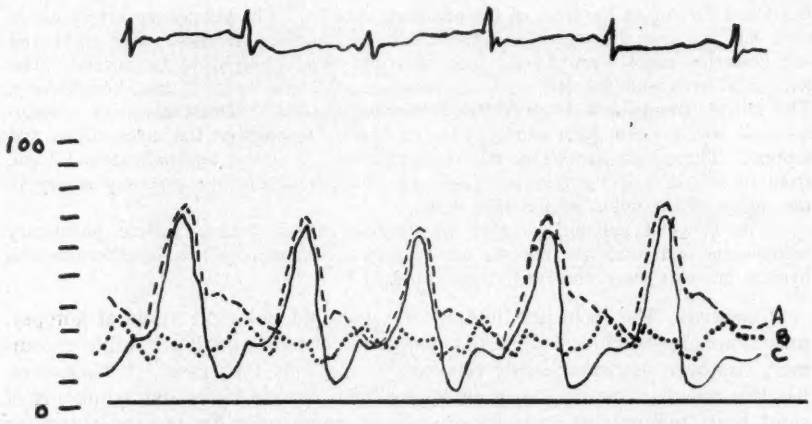

FIG. 3B. Superimposed pulmonary artery (A), right ventricular (C), and right atrial (B) pressure tracings.

from the right atrium, and (3) distensibility of the ventricle. During diastole the right ventricle is receiving blood from two sources—pulmonary artery and right atrium—and apparently reaches its capacity early, as indicated by the rapid rise in pressure. The decreased distensibility of the chamber which results from hypertrophy plays an important role in reducing the capacity of the chamber. The right atrial curve rises proportionately to assure flow from the atrium to the ventricle. In keeping with the regurgitation from the pulmonary artery, the diastolic pressure in the artery approaches the end-diastolic pressure of the ventricle. Accordingly, the isometric contraction phase is markedly reduced, and actually is hardly measurable in our tracings.

The ventricular pressure tracing recorded in this patient simulates that seen in constrictive pericarditis (figure 4). Indeed, the latter was suspected in this patient, but this possible diagnosis was eliminated by operative exploration.

Similar ventricular pressure tracings have been recorded in tricuspid regurgi-

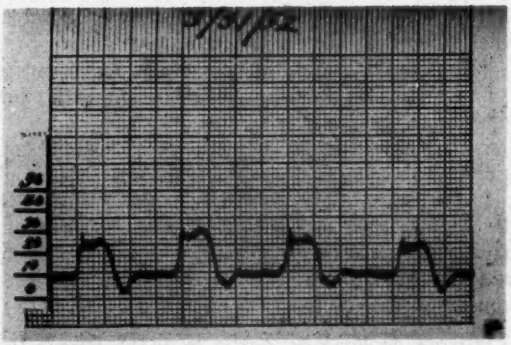

FIG. 4. The right ventricular pressure tracing in a case of constrictive pericarditis.

tation and congestive failure. In the latter, however, an early diastolic dip with plateau formation is infrequently seen. More typical, in our experience, is a general rise to a high level, which infrequently approaches the values seen in constrictive pericarditis or pulmonary regurgitation.

It is of interest that experimentally [15] the pulmonary artery diastolic pressure did not approach or equal the right ventricular diastolic pressure until pulmonary hypertension was induced in addition to the valvectomy. The present case might seem to represent a clinical example of this experimental occurrence. In this patient the anomalous bicuspid valve probably existed with or without minimal pulmonary insufficiency and without clinical cardiac deterioration until the development of the pulmonary arteriolar disease. The resulting pulmonary hypertension probably induced or increased the already existing pulmonary insufficiency across the abnormal pulmonic valve. It is of interest that chronic pulmonary disease was also present in the other two cases above,[8, 10] in which the pulmonary regurgitation was unassociated with other cardiac defects.

The concept of "functional" pulmonic insufficiency secondary to pulmonary hypertension has long been entertained. The clinical examples reported have been accompanied by little conclusive supporting evidence, since the finding of a dilated pulmonic ring at autopsy does not reflect the state of the pulmonic valve during life. It was felt that significant pulmonic insufficiency, organic or relative, might produce the characteristic changes in the right heart pressure tracings. Accordingly, the tracings were reviewed in a group of patients with evidence of severe pulmonary hypertension in whom early diastolic murmurs were heard, and there was no evidence of aortic insufficiency. The diagnoses were mitral stenosis, atrial septal defect, primary pulmonary hypertension and aortic septal defect. In many of these cases the pulmonary artery and right ventricle were likewise examined at surgery. In none of those patients did the pulmonary artery or right ventricular pressure tracings resemble those of the present case. The pulmonary artery diastolic pressure did not approach the right ventricular diastolic pressure in any, nor was there a rapid drop in the dicrotic limb of the pulmonary artery systolic pressure tracing.

It is therefore suggested that the existence or importance of so-called "functional" pulmonic insufficiency is questionable in the presence of normal valves. It is further suggested that the recording of characteristic pressure tracings in the right heart is consistent with significant pulmonic regurgitation of probable organic origin in the presence of normal or elevated pulmonary artery pressure.

Summary

1. A case of dynamic pulmonary regurgitation associated with a bicuspid pulmonic valve is reported, the second such case to be diagnosed during life by cardiac catheterization.

2. The pulmonary artery and right ventricular pressure tracings are discussed. Characteristic changes can be demonstrated in the presence of significant regurgitation.

3. It is suggested that the effect of pulmonary hypertension upon the dynamics of the pulmonic valve may be important only in the presence of an abnormal valve. It was noted that cases of "functional" pulmonary insufficiency did not show characteristic pressure tracings.

Summario in Interlingua

Grados dynamicamente significative de regurgitation pulmonar de origine organic es un occurrentia infrequente. Datos necroptic que confirmava le presentia de un valvula anormal esseva disponibile in solmente un ex cinque recentemente reportate casos in que le insufficientia pulmonar esseva diagnosticate ante morte. In nostre caso le diagnose esseva supportate per exploration chirurgic durante le vita del patiente e per le demonstration de un valvula anormal al necropsia. Le patiente—un feminina de 46 annos de etate—esseva hospitalisate con le gravamines de dyspnea in effortio, de edema malleolar, tumescentia abdominal, e orthopnea de tres annos de duration. Al tempore del hospitalisation le patiente presentava signos de disfallimento, un corde allargate con rhythmo de galopo, e al longo del margine sinistro-sternal un murmure systolic rauc del grado II e un simile murmure prodiastolic. Nulle derivation intracardiac esseva demonstrate per catheterisation cardiac, e le registrationes del pression suggereva pericarditis constrictive. In thoracotomia exploratori, un fremito diastolic esseva palpabile supra le allargate arteria pulmonar e le ventriculo dextere. Illo se diminueva quando le arteria pulmonar esseva constringite. Le impulso del secundo sono pulmonic se augmentava. Esseva constatate que le valvula pulmonic esseva insufficiente. Isto esseva constatate per un examine digital. Nulle altere lesiones intracardiac o pulmonar esseva demonstrate. Al necropsia cinque menses plus tarde, le valvula pulmonar habeva un circumferentia de 7.0 cm. Le cuspide anterior esseva normal. Le cuspides dextero- e sinistro-posterior esseva fusionate, sed il pareva que illos esseva histologicamente normal. Arteriolosclerosis pulmonar esseva presente.

Ben que pulmonic valvulas bicuspide ha essite reportate como constatation incidente al necropsia, le association de regurgitation dynamic ha essite rar. Alterationes in le registration del pression dextero-cardiac pote esser demonstrate in casos de regurgitation significative. Le alterate registration dextero-ventricular reflecte le alterate relation inter pression e volumine in le ventriculo, particularmente quando le ventriculo es hypertrophiate e providite de duo fontes de influxo, le atrio dextere e le arteria pulmonar. In regurgitation le pression diastolic del arteria pulmonar approcha le pression termino-diastolic del ventriculo. Iste ultime phenomeno occurre etiam post le production experimental de hypertension pulmonar. Es postulate que in le presente caso le anormalitate de un valvula bicuspide pre-existeva probabilemente con o sin grados minimal de insufficientia e que le regurgitation significative e le deterioration cardiac occurreva solmente post le disveloppamento del morbo pulmono-arteriolar. Le registrationes de pression obtenite ab un gruppo de patientes con murmures prodiastolic e indicios de sever hypertension secundari a congenite o acquirite morbo cardiac non esseva simile al registrationes obtenite in le caso del presente reporto. Es presentate le idea que le existentia de insufficientia pulmonic "functional" es questionabile in le presentia de un valvula normal e que le obtention de characteristic registrationes de pression per catheterisation dextero-cardiac indica un origine organic.

BIBLIOGRAPHY

1. Olesen, K. H., and Fabricius, J.: Pulmonic valvular regurgitation during twenty-seven years after gonorrheal endocarditis, Am. Heart J. **52**: 791, 1956.
2. Kohout, F. W., and Katz, L. N.: Pulmonic valvular regurgitation, Am. Heart J. **49**: 637, 1955.
3. Ford, A. B., Hellerstein, H. K., Wood, C., and Kelly, H. B.: Isolated congenital bicuspid pulmonary valve, Am. J. Med. **20**: 474, 1956.
4. Morton, R. F., and Stern, T. N.: Isolated pulmonic valvular regurgitation, Circulation **14**: 1069, 1956.
5. Kjellburg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of congenital heart disease, 1955, Year Book Publishers, Inc., Chicago.

6. Koletsky, S.: Congenital bicuspid pulmonary valves, Arch. Path. **31**: 338, 1941.
7. Ingham, D. W.: Congenital malformations of the pulmonic and aortic valves, Ann. Int. Med. **12**: 609, 1938–39.
8. Schwartz, S. P., and Shelling, D.: Acquired rheumatic pulmonic stenosis and insufficiency, Am. Heart J. **6**: 568, 1930.
9. Grawitz, E.: Zwei seltene Falle von Incontinenz des Ostium pulmonale, bedingt durch Fehlen eines Klappensegels, Virchows Arch. f. path. Anat. **110**: 426, 1887.
10. Stintzing, R.: Ueber ein seltene Anomalie der Pulmonalklappen, Deutsches Arch. f. klin. Med. **44**: 149, 1888–89.
11. Paget, J.: On obstructions of the branches of the pulmonary artery, Med. Chir. Tr., London **27**: 162, 1844.
12. Kissin, M.: Pulmonary insufficiency with a supernumerary cusp in the pulmonic valve, Am. Heart J. **12**: 206, 1936.
13. Barger, A. C., Roe, B. B., and Richardson, G. S.: Relationships of valvular lesions and of exercise to auricular pressure, work tolerance, and to development of chronic congestive failure in dogs, Am. J. Physiol. **169**: 384, 1952.
14. Blount, G. S., McCord, M. C., Mueller, H., and Swan, H.: Isolated valvular pulmonic stenosis—clinical and physiological response to open valvuloplasty, Circulation **10**: 161, 1954.
15. Fowler, N. O., Mannix, E. P., and Noble, W.: Some effects of partial pulmonary valvectomy, Circulation Res. **4**: 8, 1956.

CYCLIC FEVER, ABDOMINAL PAIN AND GRAND MAL SEIZURES: CASE REPORT *

By Richard L. Naeye, M.D., *New York, N. Y.*

Introduction

In recent years a number of periodic disorders have attracted considerable interest.[1, 2] These recur over long periods of time without apparent deterioration of health. The variety of disease patterns and number of involved systems suggest multiple influences. Hereditary, infectious, endocrinologic, allergic and neurogenic causes have been suggested, but seldom confirmed. This report is concerned with a patient in whom three periodic disorders are shown to have coexisted over a period of more than 20 years. These are: (1) bouts of cyclic chills and fever; (2) episodes of acute abdominal pain, and (3) grand mal seizures. Certain features of these disorders suggest a neurogenic origin.

Case Report

Chills and Fever: The patient was a married man, age 32, who came of healthy stock with no family history of epilepsy or other nervous disorders. There had been no known trauma at birth, and he had been well until five months of age, when he experienced sudden onset of chills and fever. The initial episode began as a severe

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chill, with temperature rising to 41°C. Thereafter, chills recurred at regular 12-hour intervals for the succeeding 10 days. No therapy was given, and from the tenth day he was free of symptoms. Similar episodes of cyclic chills reappeared at about six-month intervals during the following 12 years (figure 1), each cycle lasting from 10 to 25 days. Later attacks gradually became less frequent and recently have occurred at intervals of from one to three years.

Since their onset these episodes have followed an unvarying pattern. When the patient was first hospitalized in 1946 the chills had been in progress for 11 days. Twelve hours preceding their onset the patient had become listless and complained of a "stiffness" in shoulders, back and neck. These symptoms had always preceded chills and fever. The episode began with a severe shaking chill at 7 a.m., a daily

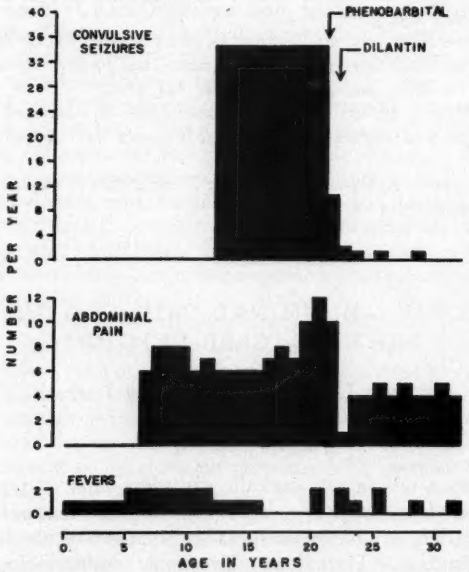

FIG. 1. The yearly incidence of febrile attacks, abdominal pain and grand mal seizures during the patient's lifetime. The influence of anticonvulsant medication started at age 20 is to be noted.

7 a.m.–7 p.m. cycle of chills being established. At the onset of each chill the nail-beds became cyanotic and the fingertips cool. With paroxysms of shaking, pilo-erection and mydriasis became prominent. During the chills, rectal temperatures gradually rose to a peak of 40° to 41°C. About one hour later drenching sweats appeared and temperatures gradually fell, reaching normal levels about seven hours after their first rise. The last chill took place seven days after admission. Ten days later the patient experienced a nocturnal generalized myoclonic seizure. This was expected, since grand mal seizures had followed previous febrile episodes. Weight loss during the febrile period totaled 15 pounds. Full recovery took three weeks.

Many attempts were made to interrupt the febrile cycles. Penicillin, chlortetracycline, salicylates and alcohol sponges were without effect. During the 1946 hospitalization the patient's sleep pattern was intentionally interrupted. On the third hospital day, instead of sleeping after the 7 p.m. chill, as was his habit, he was kept awake until midnight. The succeeding chill did not then appear the next morning at

7 a.m., as expected, but at noon. Subsequent chills followed a midnight-noon schedule. This influence of sleep suggested that a neurologic disturbance might be at fault. An attempt was made to interrupt such a mechanism during an episode which was studied in October, 1955. Intramuscular phenobarbital was administered at varying intervals before expected chills. Although sometimes delayed, the anticipated chills were not prevented. A third episode which received study began in June, 1956. Meprobamate and intravenous aminophylline failed to abort the febrile cycles. The last chill appeared 48 hours after cortisone had been started. This, however, was on the twenty-first day of the episode. Since previous episodes had ceased spontaneously in 21 days or less, the role of cortisone was uncertain.

During all three episodes studied, general physical and neurologic examinations were normal. Routine blood counts were normal except for leukocytosis. This was recorded during all phases of the chill-and-fever cycles, the average count being 25,000. A large percentage of polymorphonuclear band forms was present. Erythrocyte sedimentation rates and C-reactive protein levels were markedly elevated. Coproporphyrin levels in the urine doubled during the febrile period. Examinations for porphobilinogen were negative. Serum electrophoresis showed moderate elevations of the $alpha_1$, $alpha_2$ and gamma globulin fractions. Plasma glucose levels did not change during any phase of the febrile cycles. Antistreptolysin titers, blood cultures, agglutination reactions for paratyphoid and typhoid bacilli, brucella and rickettsial antibodies, tests for cold agglutinins and heterophil antibodies, cutaneous reactions to coccidioidin, histoplasmin and old tuberculin, and Wassermann reactions of blood and spinal fluid were negative. Routine examinations of urine and feces, including repeated cultures, showed nothing abnormal. Spinal fluid revealed only a slight protein elevation. Measurements of hepatic and renal function were normal, as were serum electrolytes. Repeated malarial and lupus erythematosus preparations were negative. While the patient was febrile, electrocardiographic examinations demonstrated elevated ST segments and diphasic T waves in precordial leads.

Abdominal Seizures: In addition to febrile episodes, the patient at age seven experienced the first of a series of acute epigastric attacks. Pain was sudden in onset, crampy in character and unremitting until relieved by morphine. Similar episodes reappeared at irregular two-month intervals during the following 13 years (figure 1). Some were preceded by premonitory symptoms. Auras were described as clamminess of the extremities, coupled with an urge to defecate. When phenobarbital and Dilantin were started at age 21, an 11 month period passed without abdominal distress (figure 1). In subsequent years abdominal episodes reappeared at about four-month intervals but, with anticonvulsant medication, diminished in both intensity and duration. A variety of therapeutic efforts, including special diets, local heat, oral sucrose and appendectomy failed to afford relief. Although unpredictable, the abdominal episodes appeared more frequently following emotional stress.

After the onset of abdominal attacks the patient's gall-bladder, kidneys and gastrointestinal tract were studied frequently by x-ray examination. These were normal until the gastrointestinal tract was studied during a severe abdominal attack. An hourglass stomach with massive gastric contraction waves was observed. Subsequent examinations during symptom-free periods have been normal.

Grand Mal Seizures: The patient experienced convulsive seizures other than those following febrile episodes. At age 12 he was noted one morning to be "staring"; this was followed momentarily by a coarse generalized tremor and unconsciousness. He then experienced a generalized convulsive seizure, with tongue biting and incontinence. It was not focal in its onset. Attacks were frequent during the succeeding eight years, occurring initially every two to three days, and later at one- to three-month intervals. He felt that they were sometimes precipitated by anger, excitement and anxiety.

At age 21 he was given phenobarbital, 30 mg. three times a day, and later Dilantin, 100 mg. three times a day. Convulsive seizures have not appeared subsequently except following fever. Electro-encephalographic recordings taken between the ages of 20 and 32 showed generally synchronous but dissimilar patterns in which abnormal slow and fast activity predominated. All were interpreted as showing persistent abnormalities consistent with a convulsive disorder. X-rays of the skull were normal.

Discussion

In all three of the disorders, premonitory symptoms suggesting auras were noted. Electro-encephalographic examinations were repeatedly abnormal. At least two of the three disorders were partially controlled by anticonvulsant drugs. There was no evidence of an endocrine, allergic disturbance or of infection. While these features suggest central origin, other features are quite unlike those described in neurogenic disturbances. For example, the patient's febrile pattern was dissimilar to fevers associated with a variety of central nervous system lesions. It was unlike the fever that often follows surgery near the pituitary fossa and the third ventricle. Penfield has reported two patients with disturbances in this region.[3] One case had widespread hypothalamic damage and the other a third ventricle tumor. Both had irregular fevers and occasional chills. Both developed paroxysmal episodes characterized by facial flush, diaphoresis, hypersalivation, increased respiratory rates, and disturbances of blood pressure, pulse rate and pupillary size. The disorganized character of these phenomena contrasts with the case here presented, in which autonomic activity followed an integrated pattern, first tending towards the conservation of heat and later contributing toward its dissipation. Patients with injuries to the upper cervical cord may also develop a protracted hyperthermia.[4] Their febrile pattern, however, is not cyclic. Anxiety and specific life stress situations can be associated with a variety of febrile patterns. None has assumed the form seen in this patient.[5, 6] Reimann has reported patients who have had periodic attacks of fever and sometimes of abdominal pain, fever and pain being recurrent at regular intervals.[1, 2] Both the predictability of recurrence and their mild course distinguish them from this case. Richter has suggested an experimental basis for periodic phenomena by demonstrating such cycles in the rat following brain lesions in the hippocampus. He has also reported cycles induced by interference with the pituitary, thyroid, parathyroid and ovarian glands.[7]

Laboratory examinations were for the most part normal. Elevated leukocyte counts, erythrocyte sedimentation rates, C-reactive protein levels and coproporphyrin levels were probably a nonspecific reflection of tissue injury consequent to prolonged hyperthermia. Temporary alterations of the electrocardiogram can also probably be attributed to hyperthermic injury. Clinical phenomena associated with the chills and fever in this case proved to be similar to those observed with the use of typhoid vaccine and in malaria.[8] As each chill began, a prominent vasoconstriction and pilo-erection appeared. A progressive rise in heart rate accompanied the chill and rising temperature, but significant changes in blood pressure did not take place. The failure of salicylates and cold sponges to alter the febrile cycles is not unusual, as exogenously induced fevers are often not affected.

In addition to chills and fever, the patient had experienced episodes of paroxysmal abdominal pain since age seven. Many features of these acute at-

tacks suggest abdominal epilepsy as described by Hoefer,[9] Moore [10] and others. Opportunities to study the visceral mechanisms associated with abdominal epilepsy have been rare. The acute abdominal pain in this patient probably originated in the massive gastric contraction waves demonstrated during one of the abdominal episodes. Hoefer reports one case in which a transient intussusception of the terminal ileum was associated with abdominal pain.[9] Since the pain associated with abdominal epilepsy is so often described as crampy, it must originate in hollow viscera, these hollow viscera often being sections of the gastrointestinal tract.[11, 12]

The unique feature of this case is the coexistence of a severe disorder of thermoregulation with abdominal epilepsy and grand mal seizures. Many features of the patient's illness suggest a neurologic disorder, but this has not been proved. A neurogenic origin is supported by the fact that a febrile cycle was altered by interruption of the patient's usual pattern of sleep. It is also striking that the patient has been well during the long periods between attacks. In addition, the onset of the disorder so early in life, its lifetime duration, its irregular recurrence and its premonitory signs suggest indirectly that a central nervous system mechanism is at fault.

Summary

A case is presented in which a patient suffered for many years with three paroxysmal disorders. These were: (a) bouts of cyclic chills and fever recurring at one- to two-year intervals; (b) episodes of acute abdominal pain appearing at intervals of from one to two months; and (c) grand mal seizures. Extensive studies failed to reveal a traumatic, hereditary, infectious, allergic or endocrine influence as cause for any of the disorders. Both the abdominal attacks and the grand mal seizures were partially controlled by anticonvulsant medication. Various empiric therapeutic attempts to halt the febrile attacks were ineffective.

Acknowledgment

The author would like to acknowledge his appreciation of the helpful criticisms of Dr. Harold G. Wolff.

Summario in Interlingua

Es demonstrate le co-existentia de tres disordines periodic in un masculo de 34 annos de etate: (1) Episodios de algor e febre cyclic; (2) occurrentias de acute dolores abdominal; e (3) accessos de grand mal. Le patiente habeva su prime sever episodio de algor e febre al etate de cinque menses. Le cyclo de algor e febre se repeteva durante le sequente 10 dies a intervallos regular de 12 horas. Simile episodios ha occurrite omne sex a 34 menses usque al tempore presente. Al etate de septe annos le patiente experientiava subite e sever crampos epigastric que esseva si dolorose que morphina esseva requirite pro alleviar los. Simile episodios se manifestava durante le sequente annos a intervallos de circa duo menses. Studios roentgenologic effectuate in le curso de un tal episodio demonstrava massive contractiones gastric. Al etate de 12 annos le patiente experientiava un generalisate accesso convulsive. Initialmente, simile attaccos convulsive se repeteva frequentemente. Depost le etate de 21 annos, le accessos de grand mal e etiam le attaccos abdominal ha essite subjugate partialmente per un medication anticonvulsori. Ancora altere characteristicas de iste disordines indica lor origine neurogene. Auras ha precedite omne tres. Le cyclos de febre poteva esser alterate sed non supprimite per le interruption del habituate periodos de

somnio. Le registrationes electro-encephalographic se ha monstrate persistentemente anormal. In despecto de extense studios, nulle influentia traumatic, hereditari, infectiose, allergic, o endocrin poteva esser identificate como causa de ulle del disordines.

Plure aspectos del dolor epigastric suggere epilepsia abdominal. Le association del dolor con contractiones gastric es significative, proque opportunitates de studiar le mechanismos visceral que es associate con epilepsia abdominal ha essite rar. Le disordine in le thermoregulation es dissimile a altere disturbationes febril que es incontrate in association con disordines neurogene. Tamen, labores experimental ha demonstrate que simile phenomenos periodic pote occurrer in association con lesiones cerebral in le hypocampo. Le caso hic presentate es unic in tanto que le grave disordine febril co-existe in illo con epilepsia abdominal e accessos de grand mal.

BIBLIOGRAPHY

1. Reimann, H. A.: Periodic disease, a probable syndrome including periodic fever, benign paroxysmal peritonitis, cyclic neutropenia and intermittent arthralgia, J. A. M. A. **136**: 239, 1948.
2. Reimann, H. A.: Periodic disease, periodic fever, periodic abdominalgia, cyclic neutropenia, intermittent arthralgia, angioneurotic edema, anaphylactoid purpura and periodic paralysis, J. A. M. A. **141**: 175, 1949.
3. Penfield, W., and Erickson, T. C.: Epilepsy and cerebral localization, 1941, Charles C Thomas, Springfield, Illinois.
4. Holmes, G.: Spinal injuries of warfare, Brit. M. J. **2**: 815, 1915.
5. Dunbar, H. F.: Emotions and bodily changes, 2nd Ed., 1938, Columbia University Press, New York.
6. Wolf, S., and Wolff, H. G.: Intermittent fever of unknown origin, Arch. Int. Med. **70**: 293, 1942.
7. Richter, C. P.: Unpublished data.
8. Perera, G. A.: Clinical and physiologic characteristics of chill, Arch. Int. Med. **68**: 241, 1941.
9. Hoefer, P. F. A., and Cohen, S. M.: Paroxysmal abdominal pain, a form of epilepsy in children, J. A. M. A. **147**: 1, 1951.
10. Moore, M. T.: Paroxysmal abdominal pain, a form of focal symptomatic epilepsy, J. A. M. A. **129**: 1233, 1945.
11. Fulton, J. F., Kennard, M. A., and Watts, J. W.: Autonomic representation in the cerebral cortex, Am. J. Physiol. **109**: 37, 1934.
12. Spiegel, E. A., Weston, K., and Oppenheimer, M. J.: Postmotor foci influencing the gastrointestinal tract and their descending pathways, J. Neuropath. and Exper. Neurol. **2**: 45, 1943.

ACUTE MENINGOCOCCEMIA WITH SYMMETRIC PERIPHERAL GANGRENE: REPORT OF A CASE WITH RECOVERY*

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The patient with acute meningococcemia and rapidly falling blood pressure presents one of the most dramatic medical emergencies physicians encounter.

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In nonepidemic areas or seasons the occasional case is likely to escape recognition until the typical purpura, disorientation and peripheral vascular collapse alert the physician to the septicemic nature of the disease. With the advent of oral and parenteral steroid therapy, death from meningococcemia, with or without severe hypotension, is now the exception rather than the rule.[1-7] That recovery can be obtained in even the most severely ill is illustrated by the following case which, in addition to the usual features of Waterhouse-Friderichsen syndrome, showed a septic, occlusive gangrene of the distal digits not frequently encountered in a recovered patient.

Case Report

A 20 year old white enlisted man was admitted to Madigan Army Hospital because of drowsiness, disorientation and purpura of two hours' duration. Three days prior to admission the patient had begun to have a sore throat. He did not report to sick call. The day before admission he played baseball and noted a few petechial spots on his extremities. The night before admission he was nauseated and faint, and vomited twice. He went to bed early and spent a restless night. Upon arising the next morning he had headache, dizziness, drowsiness, chilly sensations, slightly stiff neck, sore mouth and patches of petechiae over all his body coalescing into purpura peripherally. His hands and feet felt stiff and swollen and ached severely.

His past history was negative for any serious diseases. He had had the usual childhood diseases, without sequelae, but no adult injuries or illnesses other than virus pneumonia without complication.

On admission the patient was drowsy, acutely uncomfortable and severely ill. He was able to respond partially to questions. Blood pressure was 76/40-0 mm. of Hg; pulse, 44 per minute; temperature, 102° F. Respirations were regular but shallow. He complained of pain in hands and feet. Peripheral pulses were all present but thready. There was a livid cyanosis of the ears, mucous membranes, lips, hands and feet. The dorsa of the hands and feet were puffy and tender. The body was literally covered with petechiae, particularly in the natural creases and pressure points. Peripherally and on the chest and trunk, petechiae were coalesced into purpuric eruptions of deep cyanotic hue. Subconjunctival hemorrhages and tiny retinal hemorrhages were visible bilaterally. The neck was slightly stiff. The pupils reacted to light and accommodation. The chest was clear to percussion and auscultation. The heart had a tic-tac rhythm with poor quality and faint heart sounds. There were no murmurs, thrills or enlargement to percussion. The abdomen demonstrated no masses or enlargement. There was tenderness over the left colon, and the patient passed a bloody liquid stool. Reflexes were active and equal.

Significant laboratory data on admission included a white count of 22,550, with 86% neutrophils, 7 lymphocytes, 6 monocytes and 3 eosinophils; platelet count, 43,000; hematocrit, 43%; bleeding time, 2 minutes 30 seconds; coagulation time, 3 minutes 40 seconds. Numerous intracellular and extracellular diplococci were visible in the Wright-stained smear of the peripheral blood. These proved to be gram-negative diplococci by gram stain of a petechial smear and to be *Neisseria meningitidis* by culture. Disc sensitivity studies showed this organism to be resistant to penicillin, but sensitive to streptomycin, dihydrostreptomycin, chloramphenicol, Aureomycin and Terramycin. Urinalysis showed a yellow cloudy fluid with neutral reaction; specific gravity, 1.012; albumin and sugar, negative; microscopic: three to five white blood cells and three to four red blood cells per high power field. Cardiolipin microflocculation was negative. Blood and throat cultures were both positive for *N. meningitidis* with heavy growth.

Hospital Course: The patient gradually lapsed into a restless coma. Forty units

of ACTH were given with 5% dextrose and distilled water intravenously while blood cultures, throat cultures and other studies were being done. A transfusion of 500 c.c. of compatible blood was begun, together with another infusion containing 5 gm. sodium sulfadiazine and 1,000,000 units crystalline penicillin. A third intravenous infusion of 500 c.c. normal saline containing 125 mg. of hydrocortisone (alcohol) was begun. By this time the patient had deteriorated neurologically and had become extremely restless, requiring 28 c.c. of intramuscular paraldehyde in a five-hour period. The blood pressure, which had fallen as low as 60/40 mm. Hg, began to rise as the infusions were given rapidly. During the first 12 hours the patient received 15 gm. of sodium sulfadiazine, 12,000,000 units of crystalline penicillin, 750 c.c. of whole blood, 2,000 c.c. 5% glucose and normal saline, 2,000 c.c. 5% glucose

FIG. 1 (*left*). June 22, 1955, third hospital day. Trunk and upper extremities: note the coalescent petechiae and purpuric areas with roughly symmetric distribution. The hands are puffy, edematous, cold and deeply cyanotic.

FIG. 2 (*right*). June 22, 1955. Lower extremities. Coalescent areas of purpura on lower legs, with edema, coldness and deep cyanosis of the toes distally.

and water, and 975 mg. hydrocortisone (alcohol) together with 40 mg. ACTH. For the entire second hospital day the patient was unconscious, but the blood pressure had recovered to levels of 110–120/94–48 mm. of Hg. The second day 625 mg. of hydrocortisone (alcohol) and 11.5 gm. of sodium sulfadiazine were given intravenously in repeated infusions. In addition, the patient received penicillin, 2,000,000 units every two hours, intravenously or intramuscularly. On the third hospital day he received 500 mg. hydrocortisone (alcohol), and intravenous penicillin and sulfadiazine were continued as before. By the fourth hospital day he had recovered consciousness and was considered out of danger clinically. However, the purpuric areas on the hands and fingers had coalesced (figures 1 and 2). The fingertips were a dead blue-black color, and were cold and painful. A stellate ganglion block failed to lessen the cyanosis of the fingertips.

From the fourth hospital day on, hydrocortisone dosage was dropped by 50% increments until all drug was stopped on the ninth hospital day. ACTH stimulation of the adrenal cortex was begun again on the fourth hospital day and continued for three days after the last hydrocortisone infusion. Adequacy of the adrenal glands was checked following ACTH stimulation from the third hospital day on through the last three days of ACTH administration. During the last three-day period, adrenal cortical adequacy was established by a fall of the total eosinophil count by

FIG. 3 (*left*). July 5, 1955, sixteenth hospital day. Trunk and upper extremities: note cutaneous sloughs on left upper arm and shoulder, also persistence of edema and cyanosis of finger-tips.

FIG. 4 (*right*). July 5, 1955, sixteenth hospital day. Note apparent line of demarcation on right great toe, with subcutaneous tissue atrophy and blackening of overlying skin.

50% or more following eight-hour intravenous administration of 20 to 40 mg. of ACTH. By the eighth hospital day all steroid therapy was discontinued. Antimicrobial therapy was discontinued after the tenth hospital day.

Twelve days after admission the patient was anxious to be up and around in a wheelchair, and three days later was largely free of pain. The lesions on the patient's arms, chest and hands healed slowly (figures 3 and 4). During the following weeks desquamation of dead skin and subcutaneous tissue proceeded at a fairly rapid rate. Atrophy of the distal phalanges of the left hand appeared to regress distally as time went on. For the open lesions, open dry treatment was allowed, the patient resting on sterile nylon bedclothes. One month after admission, atrophy of the distal phalanges of the left second, third and fourth fingers and of the right great toe appeared stable,

with distinct lines of demarcation of gangrenous areas distally. It was elected to wait for self-amputation to occur in order that maximal soft tissue could be saved. The patient was able to be up on crutches 10 weeks after admission. Adrenal function studies, including eosinophil count and 17-ketosteroid excretion after eight hours of ACTH infusion, were normal at this time. The patient was transferred to the orthopedic service three months after admission. One month later partial amputa-

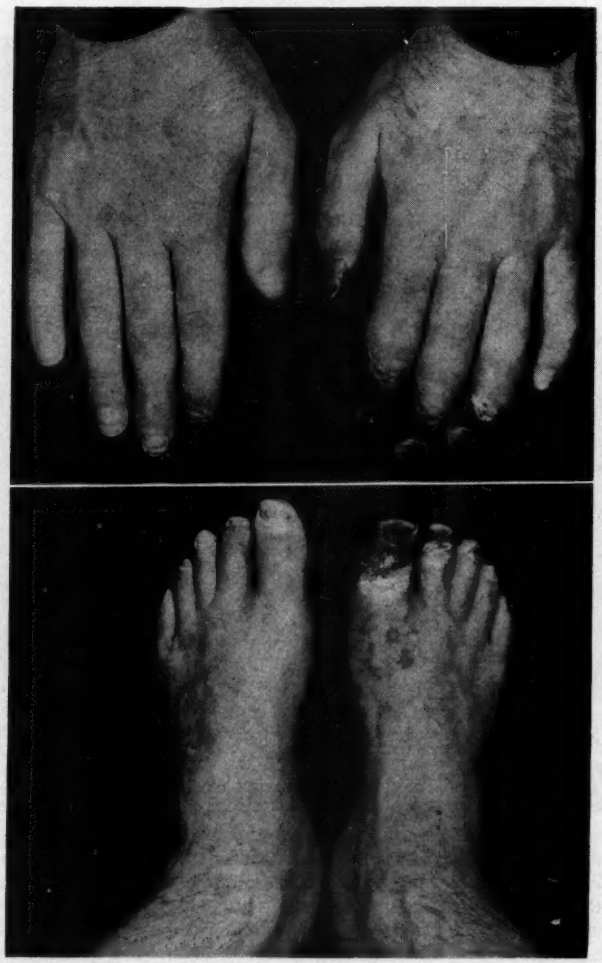

FIG. 5 (*above*). October 14, 1955, one hundred seventeenth hospital day. Eschars of skin of distal fingers with subcutaneous atrophy, more marked on the left. The line of demarcation is more apparent than real, since all phalanges remain except the distal phalanx of the right index finger, which later amputated spontaneously.

FIG. 6 (*below*). October 14, 1955, one hundred seventeenth hospital day. Sparing of nails and subcutaneous tissue and healing of skin underlying eschars. All digits were saved and there was no residual arthropathy.

tion of the distal phalanges of the right great toe and of the left index finger was performed. All other areas had healed normally (figures 5 and 6) prior to surgery.

Discussion

Despite the classic nature of this patient's presenting symptoms and signs, the diagnosis was very nearly missed because of the attending physician's preoccupation with the low platelet count. It was only after the peripheral blood smear was examined closely a short while later that the meningococcemia was recognized. Such an error could have been fatal.

The use of such massive doses of intravenous hydrocortisone as 1,000 mg. the day of admission may seem excessive until it is remembered that this man appeared moribund. Also, while the use of ACTH late in the course may have been unnecessary, it seemed desirable to prove the adrenal glands capable of responding to ACTH stimulation before discontinuing antimicrobial therapy and discarding hydrocortisone support entirely. It is felt that the doses of steroid used were not excessive but simply adequate for a patient with such a severe septicemia in whom the adrenal glands were most likely incapable of adequate response to endogenous ACTH.

The finding, in the midst of therapy, that this strain of *N. meningitidis* was resistant to penicillin by disc sensitivity method did not alter the penicillin therapy in this patient. However, it must be noted that sulfadiazine remains the drug of choice in the treatment of meningococcemia.[8-10] The patient was well before anybody thought to do a lumbar puncture.

Fishberg originally reported symmetric gangrene as an occurrence in acute right heart failure.[11] It has since been reported as a complication of peripheral vascular collapse associated with overwhelming infections, and in shock associated with myocardial infarction.[12-15] The symmetric gangrene recorded in this case may be due in part to the peripheral vascular collapse associated with the septicemia and adrenal cortical insufficiency. However, it must be considered that the septic thrombi which produced the petechiae and purpuric areas elsewhere in the body were probably aggregated in larger amounts in the slower-flowing vascular nets of the peripheral skin and subcutaneous tissues of the hands and feet. Pathologists have suggested that the vasa vasorum in these areas become plugged with large bacterial colonies, resulting in vascular wall necrosis and localized hemorrhage.[16] It is also suspected that such clots occluded the distal fingertip and toe arteries.

Meningococci apparently share with other gram-negative organisms and some rickettsiae the propensity to cause cutaneous sloughs and thrombotic gangrene. Present thinking is that antimicrobial therapy releases large amounts of organism endotoxin into tissues previously sensitized to the live meningococcal endotoxin, thereby producing a Shwartzman phenomenon. Thus, the presence of live bacteria in the distal end-arteries is not required for tissue necrosis to occur.[17] This patient's lesions, though large, did not require skin grafting but were allowed to granulate and epithelialize from the periphery.

The patient did not receive any vasopressor substances or any adrenal cortical extracts other than those recorded in the protocol. Had such been used, they would have been blamed for the occlusive peripheral gangrene. It would appear that hydrocortisone (alcohol) in adequate amounts represents ade-

quate replacement therapy for a patient with acute adrenal cortical insufficiency of severe degree.

Summary

A case of acute meningococcemia in a previously healthy male is recorded in which the presenting evidences of severe hypotension determined a diagnosis of adrenal cortical insufficiency. Severity of the process was evidenced by bilateral symmetric peripheral gangrene. Immediate improvement and permanent recovery followed the use of intravenous hydrocortisone (alcohol) in addition to antimicrobial and supportive therapy.

Summario in Interlingua

Il es a expectar que casos sporadic de meningococcemia acute escappa al recognition usque le manifestationes typic de purpura, disorientation, e collapso peripherovascular demonstra al medico le natura septicemic del condition. In casos recognoscite, exito mortal ha devenite incommun gratias a therapia steroide per via oral o parenteral. Es presentate le caso de un soldato de racia blanc de 20 annos de etate qui esseva admittite al Hospital Militar Madigan con somnolentia, disorientation, e purpura de un duration de duo horas. Le examine al tempore del admission revelava febre, bradycardia, e un pression sanguinee de 76/40 mm de Hg. Cyanosis livide se manifestava al aures, membranas mucose, labios, e pedes. Petechias e ecchymoses coalescente esseva presente in omne regiones del corpore. Culturas ab le lesiones cutanee, le sanguine, e le gurgite revelava le presentia de *Neisseria meningitidis*. Le stato de choc respondeva solmente a grandissime doses intravenose de acetato de hydrocortisona. Le meningococcemia esseva tractate con sulfadiazina e penicillina per via parenteral. Le patiente redeveniva conscie in circa 43 horas. Un aspecto remarcabile—a parte le relativemente grande doses parenteral de steroide requirite—esseva le gangrena bilateral symmetric del digitos de mano e pede. Es supponite que isto esseva le effecto de obstruction bacterial del arterias terminal e possibilemente etiam le effecto del phenomeno de Shwartzman.

BIBLIOGRAPHY

1. Nelson, J., and Goldstein, N.: The nature of the Waterhouse-Friderichsen syndrome, J. A. M. A. **146**: 1193–1197, 1951.
2. Wheeler, D., and Amidon, E. I.: Waterhouse-Friderichsen syndrome, New England J. Med. **247**: 256–258, 1952.
3. Breen, G. E., Edmond, R. T. D., and Walley, R. V.: The Waterhouse-Friderichsen syndrome treated with cortisone, Lancet **1**: 1140–1142 (June 7) 1952.
4. Uhl, H. S. M.: Nor-epinephrine in the treatment of acute meningococcemia with shock (Waterhouse-Friderichsen syndrome) and an evaluation of adrenocortical function, New England J. Med. **249**: 229, 1953.
5. Hodes, H. L., Moloshok, R. E., and Markowitz, M.: Fulminating menincococcemia treated with cortisone: use of blood eosinophil count as a guide to prognosis and treatment, Pediatrics **10**: 138, 1952.
6. Griffin, J. W., and Daeschnor, C. W.: Meningococcal infections: with particular reference to fulminating meningococcemia (Waterhouse-Friderichsen syndrome) treated with cortisone and nor-epinephrine, J. Pediat. **45**: 264, 1954.
7. Tobin, J. L.: Complications of meningococcal infection in a series of sixty-three consecutive sporadic cases, Am. J. M. Sc. **231**: 241, 1956.

8. McCrumb, F. R., Hall, H. E., Meredith, A. M., Deane, G. E., Minor, J. V., and Woodward, T. E.: Chloramphenicol in the treatment of meningococcal meningitis, Am. J. Med. **10**: 696, 1951.
9. Etteldorf, J. N.: Management of purulent meningitis, J. A. M. A. **159**: 746, 1955.
10. Alexander, H. E.: Guides to optimal therapy in bacterial meningitis, J. A. M. A. **152**: 662, 1953.
11. Fishberg, A. M.: Redistribution of blood in heart failure, J. Clin. Investigation **17**: 510, 1938.
12. Storstein, O.: Incipient symmetrical peripheral gangrene complicating pneumonia, Brit. Heart J. **13**: 411, 1951.
13. Swan, W. G. A., and Henderson, C. B.: Peripheral gangrene in myocardial infarction, Brit. Heart J. **13**: 68, 1951.
14. Bird, T., Leithead, C. S., and Lowe, K. G.: Symmetrical peripheral gangrene in low-output heart failure, Lancet **2**: 780, 1954.
15. Caserte, S. J., Metz, R., and Anton, M.: Symmetrical peripheral gangrene in myocardial infarction, New England J. Med. **254**: 568, 1956.
16. Boyd, W.: A textbook of pathology, 1953, Lea and Febiger, Philadelphia.
17. Woodward, T. E.: Clues to better understanding of the nature and treatment of certain infectious diseases, Am. J. M. Sc. **231**: 369, 1956.

CARDIOVASCULAR COMPLICATIONS OF PAGET'S DISEASE: A CASE REPORT *

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PAGET'S disease is one of the most frequently encountered bone disorders, and the emphasis in the voluminous literature on the subject has been on the osseous changes. Less well known, and until relatively recent years rarely recorded, are the cardiovascular complications, of which the following case is a graphic example.

CASE REPORT

The patient was a 29 year old male of Italian extraction in whom Paget's disease had first been diagnosed 11 years before, when he was treated for a spontaneous fracture of the elbow. The diagnosis was subsequently confirmed by a bone biopsy. The course of the bone disease following initial discovery was that of continuous progression to extensive involvement of practically the entire skeletal system. In January, 1956, he began to complain of dyspnea on effort. Increasing severity of this respiratory discomfort was the immediate reason for his visit to the clinic.

On examination the patient exhibited moderate tachypnea at rest. There were marked enlargement and bossing of the head, with prominent, tortuous temporal vessels. The skin overlying all the afflicted bones was warm to the touch. In the recumbent position the cervical veins were engorged and the antecubital veins were tense, even in the partially elevated arm. There was an increase in the A-P diameter of the chest. The heart was markedly enlarged, the apex reaching in the

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sixth interspace to the anterior axillary line. The rhythm was regular and the rate was 110 per minute. A soft, blowing systolic murmur was heard at the apex. The sounds were of fair quality. The blood pressure was 160/60 mm. of Hg. The lungs were clear to percussion and auscultation. The liver was not enlarged, and there was no peripheral edema. X-ray studies showed extensive pagetoid changes of practically all the bones. The tibial bones were relatively uninvolved. Figures 1 and 2 show the marked involvement of the skull and pelvis. Radiographic and fluoroscopic examination of the heart revealed considerable enlargement, principally in the region of the left ventricle. Figure 3 is a photograph of a film of the chest taken in 1952, for comparison with size of heart noted in figure 4, a reproduction of

FIG. 1. Photograph of an x-ray of skull, showing extensive pagetoid changes.

a film taken in 1956. A laboratory finding of note was an alkaline phosphatase level of 189 King-Armstrong units. The electrocardiogram showed a sinus tachycardia with low voltage T_5 and T_6. A circulation time using calcium gluconate was 9 seconds. Venous pressure in the left antecubital vein measured 17 cm.

The patient was digitalized and his activity restricted. The effectiveness of the régime could not be evaluated, since he moved out of the city shortly after the therapeutic program was started.

DISCUSSION

Wagner [1] in 1947 submitted a report on this patient as an instance of the youngest case of Paget's disease recorded. A thorough search of the literature

to date has revealed no reports that would challenge this claim. The usual age incidence, as is well known, is in the declining years of life.

The predominant feature of the present clinical picture was the cardiovascular complications. The syndrome as manifested by increased venous pressure, rapid circulation time, tachycardia, cardiac enlargement, and, finally, cardiac failure, fulfills simple criteria for high output failure. This latter may be defined as congestive heart failure in the presence of increased cardiac output. In Paget's disease, increased cardiac output stems from the markedly increased vascularity of affected bones. Sir James Paget,[2] in his original description of the disease, called attention to this marked vascularity. Others [3] have since confirmed this

FIG. 2. Photograph of an x-ray of pelvis, showing extensive pagetoid changes.

finding and related it to the cardiovascular complications of the disorder. Moore [4] in 1923 showed that the blood flow in an affected limb was considerably greater than that found in a sound limb. Edholm et al.[5] in 1945 measured the cardiac output and bone blood flow in an elderly man with advanced bone disease complicated by heart failure. The output was found to be 13.3 L./min., as compared to the normal 4 L./min. Exclusion of the extensively involved limbs by tourniquet caused a significant drop in this figure. They concluded that in generalized Paget's disease an increase in blood flow occurs of sufficient magnitude to produce an effect in the general circulation similar to that resulting from free arteriovenous communication. The increased cardiac workload ultimately exhausts cardiac reserve and leads to heart failure. These pathophysiologic facts were readily demonstrable in the case recorded here. The increased vascu-

larity of the affected bones was palpably evident in the increased temperature of the overlying skin. This marked vascularity, functioning in effect, as noted, like an arteriovenous fistula, shunted an appreciable part of the cardiac output directly from the arterial to the venous circulation, bypassing the larger and more slowly moving capillary circulation. The clinical picture that evolved was the sum total of the effects of such a shunt on the cardiovascular hemodynamics. The initial effect was augmented venous return under increased pressure, clinically manifested by increased venous pressure and rapid circulation time. Increased venous return of necessity led to increased cardiac output, which was accomplished chiefly by enhanced stroke output and accelerated heart rate. The tachycardia has been attributed to a Bainbridge reflex due to increased venous return and consequent increased right atrial pressure. Increased stroke output was responsible for a rise in systolic pressure, while diminished peripheral resistance, engendered by a leak in the piping system at the open vascular spaces in the diseased bones, depressed the diastolic pressure. The sum total was an increase in pulse pressure, as was noted in this case. Increased cardiac output in time led to cardiac enlargement and finally to heart failure, which dominated the clinical picture in this case. Despite the development of heart failure, the circulation time remained rapid, the short circuiting more than compensating for the prolongation that usually results from decompensation.

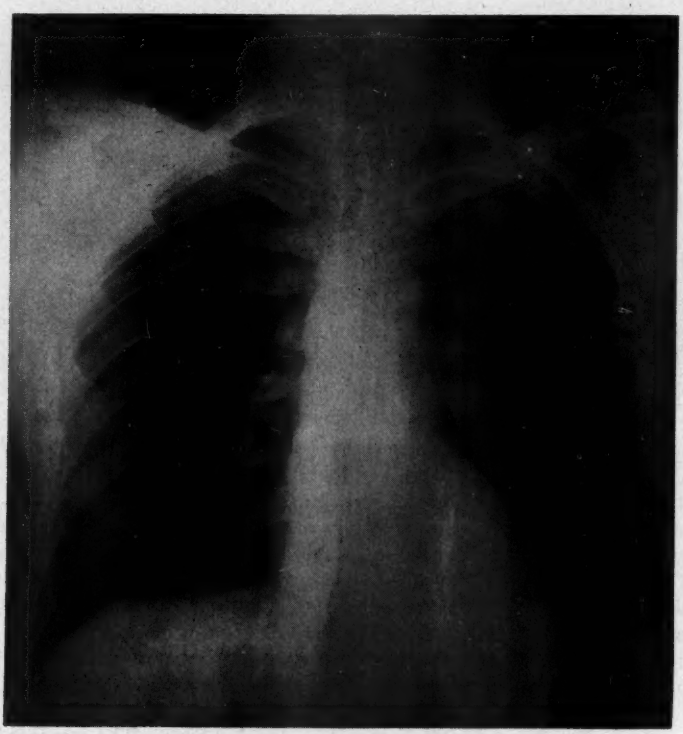

FIG. 3. Photograph of x-ray of chest, showing the size of heart in 1952.

FIG. 4. Photograph of x-ray of chest, showing size of heart in 1956.

SUMMARY

A case is presented of generalized Paget's disease developing in an 18 year old male, complicated 11 years later by cardiac failure. The clinical syndrome graphically depicted the pathologic physiology of the high output heart failure that evolved primarily from the increased vascularity of the affected bones.

SUMMARIO IN INTERLINGUA

Es presentate un caso de morbo de Paget con complicationes cardiovascular. Le disordine comenciava in 1945,* al extraordinarimente juvene etate de 18 annos, e sequeva subsequentemente un curso irresistibilemente progressive, afficiente le plus extensemente quasi omne partes del systema skeletic. In januario 1956, symptomas de un reducite reserva cardiac se disveloppava, manifeste in augmentate grados de dyspnea post exercitio.

Al presentation le patiente habeva 29 annos de etate. Ille esseva un masculo italian, exhibiente le aspectos characteristic de generalisate morbo pagetoide. Ille esseva tachypneic, e le venas cervical esseva distendite. Allargamento cardiac esseva manifeste. Le rhythmo esseva de origine sinusal. Le frequentia esseva alte. Le pression sanguinee esseva 160/60 mm de Hg. Le datos laboratorial indicava que le phosphatase alcalin esseva elevate a 189 unitates de King-Armstrong. Le tempore del circulation esseva 9 secundas, e le pression venose esseva 17 cm. Studios roent-

* A ille tempore le caso esseva reportate per Wagner.[1]

genographic revelava extense affectiones ossee e allargamento del silhouette cardiac. Assi le predominante aspecto clinic esseva un extense affection pagetoide con complicationes cardiovascular characteristic de disfallimento cardiac a alte rendimento.

Es signalate que le marcate augmento del vascularitate del ossos affligite produceva in le circulation general le effecto de libere communicationes arterio-venose. Le consequente augmento del retorno venose resultava in un augmento del rendimento cardiac. In le curso del tempore, con le non-diminuite progresso del morbo ossee, allargamento cardiac debeva sequer con le resultato final de disfallimento cardiac. Assi le hic describite constatationes clinic in le presente caso provide un delineation graphic del physiologia pathologic de iste syndrome, i.e. un disfallimento a alte rendimento que resultava primarimente ab le augmentate vascularitate del ossos afficite.

BIBLIOGRAPHY

1. Wagner, M.: Report of a case of Paget's disease in an 18 year old male, with review of literature, Wisconsin M. J. **46**: 1098, 1947.
2. Paget, J.: On a form of chronic inflammation of bones (osteitis deformans), Med.-Chir. Tr. London **60**: 37, 1877.
3. Sornberger, C. F., and Smedal, M. L.: Cardiovascular changes in Paget's disease, Circulation **6**: 711–726 (Nov.) 1952.
4. Moore, S.: Osteitis deformans, Am. J. Roentgenol. **10**: 507, 1923.
5. Edholm, O. G., and McMichael, J.: Heart failure and bone blood flow in osteitis deformans, Clin. Sc. **5**: 249, 1945.

PULMONARY VEIN OBSTRUCTION: AN UNCOMMON SEQUEL TO CHRONIC FIBROUS MEDIASTINITIS *

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The mediastinum in health is an extremely mobile and adaptable space lined by a minimum of connective tissue which binds together the heart, great vessels, esophagus, trachea, lymphatic channels and the phrenic and vagus nerves. This adaptability to the changes in size, shape and position of the mediastinal structures may be seriously impaired by various pathologic processes, including inflammation and neoplasm. Thus, in chronic mediastinitis, the laying down of dense connective tissue may lead to the production of striking and dramatic symptom complexes as a result of compression of one or more of these structures. Some of the sequelae of this condition have been known for a long time, and vascular obstruction due to fibrous or indurative mediastinitis was noted by Hare [1] in 1889 and by Osler in his *Principles and Practices of Medicine*.[2]

The case described below is one of obstruction of the pulmonary veins secondary to chronic fibrous mediastinitis. This disturbance is one of the less commonly known vascular complications of this disease. It is the purpose of

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this report to describe the events arising from this rare sequel to mediastinitis, and to discuss and call attention to the poorly appreciated underlying illness and the other clinical syndromes which it may produce.

Case Report

The patient was a 25 year old Negro, a gasoline station attendant, who was admitted to the hospital on November 12, 1954, with complaints of recurrent "asthma" and hemoptysis of approximately one month's duration. In October, 1954, while at work, he had had a sudden episode of cough which persisted for three or four days and then subsided. Several weeks later the patient was wakened from sleep by a paroxysm of cough productive of large amounts of bright red blood. Tightness in the chest and oppressive shortness of breath were also present. He was treated with antibiotics by his local physician for about a week and, when symptoms persisted, was referred to the clinic of a community hospital, where a chest roentgenogram resulted in a diagnosis of bilateral upper lobe bronchopneumonia. The patient remained at bed rest for four or five days and received Aureomycin. Since there was no response to this therapy he was referred to this institution for further study.

Past history revealed that at eight years of age the patient had been admitted to a hospital for treatment of a respiratory illness of some seven weeks' duration. The hospital abstract indicated that coarse râles with roughened breath sounds were heard over both lung fields, and reddening of the mucosa of the posterior pharyngeal wall was noted. Pneumococci and staphylococci were the predominating organisms in the throat cultures. The white blood count was 18,000, with 89% polymorphonuclear leukocytes. The patient was treated symptomatically and discharged following an uneventful recovery with the diagnosis of acute bronchopneumonia. Except for this episode, he could recall no other significant childhood illness. However, in later childhood, mild, nondisabling respiratory distress was noted on exertion which in no way interfered with his boyhood activities. He volunteered, nevertheless, that he did become more short of breath and tired more easily than did the other boys his age. The patient was inducted into the U. S. Army in January, 1951, and had some difficulty in basic training because of the development of dyspnea on hikes and other physical exertion. He was transferred from company to company and on several occasions was accused of "goldbricking." After finishing basic training he was transferred to Austria and managed well for the next seven or eight months on light and sedentary duties. He was then assigned to a construction engineering unit and one day, while climbing a rope, suffered a sudden, severe paroxysm of dyspnea and cough productive of bright red blood. He was treated at a dispensary for several days and when symptoms abated was sent back to a job which required no strenuous activity. During the remainder of his time in service the patient continued to complain of cough, "colds," shortness of breath, excessive perspiration, and periodic episodes of mild hemoptysis. He visited sick call several times weekly and received numerous penicillin injections but was told that no serious ailment was present. In January, 1953, on completion of his tour of duty, he received a regular honorable discharge. Though the patient did relatively well for the next 19 months and was able to work steadily in a gasoline station, he did visit his local physician on three or four occasions because of bouts of acute dyspnea and a single episode of hemoptysis. He was treated with pills and injections and told that he had asthma. In the intervening periods, continuous shortness of breath was present but was not severe enough to require medical attention.

There was no history of tuberculosis or tuberculosis contact, rheumatic fever, hypertension, bleeding tendency or venereal disease. The patient had lost 40 pounds in the six months prior to admission.

Physical examination at the time of admission revealed a well developed, well nourished young Negro who was dyspneic at rest. Respiratory rate was 24 per minute. Pulse rate was 72 per minute and the rhythm was regular. There was no cyanosis or clubbing of the fingers. Examination of the chest was negative except

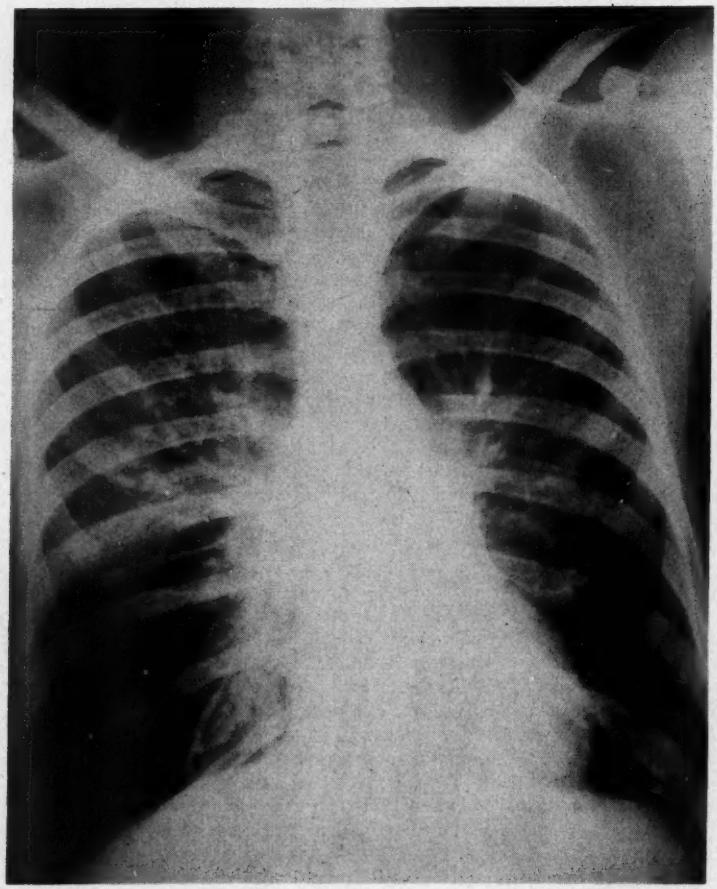


FIG. 1. X-ray of chest on admission. Note abundance of vascular markings in upper lung fields as compared to lower, and the prominent pulmonary conus.

for loud wheezes heard throughout both lung fields. No cardiac abnormalities were noted by the admitting physician, and no abdominal organ enlargement or masses could be detected. There was no peripheral edema.

Laboratory and X-Ray Data: Urinalysis revealed no abnormalities. Serologic test for syphilis was negative. Hemoglobin shortly after admission was 14 gm., with a red cell count of 4.8 million and a hematocrit of 49%. The white cell count was 19,000, with 82% polymorphonuclear leukocytes. No eosinophilia was noted. Serial studies throughout the period of hospitalization showed no significant change except

for a drop in the white cell count to within normal limits. Other studies, including bleeding time, clotting time, prothrombin time, blood urea nitrogen, CO_2 combining power and serum chlorides, were normal. Bacteriologic examination of the sputum for pathogens and tubercle bacilli was negative.

X-ray of the chest on admission revealed an increase in pulmonary vascular markings which was greatest in the upper lobe regions. There was marked prominence of the hilar segments. Heart size was within normal limits, but there was definite prominence of the pulmonary conus (figure 1). Serial x-ray studies during the period of hospitalization showed no significant change. No parenchymal lesions were demonstrated at any time.

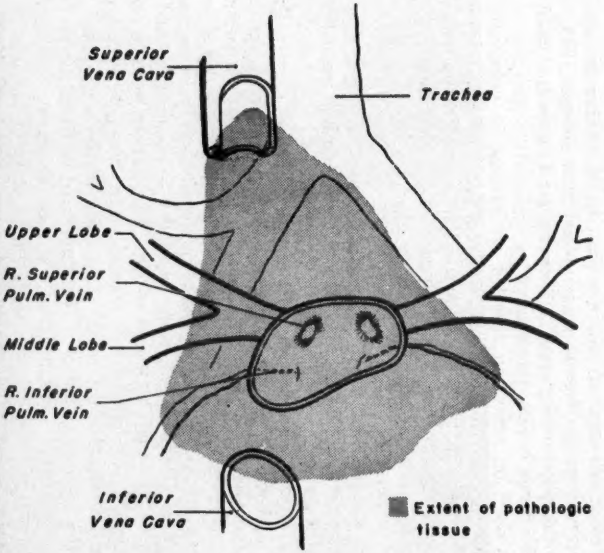
Repeated electrocardiograms revealed right axis deviation and a sinus rhythm. The usual pattern suggested chronic cor pulmonale, but during acute symptomatic periods the pattern of an acute cor pulmonale appeared.

Course in Hospital: The patient was first admitted to the Tuberculosis Service. During the initial 72 hours he did not appear to be in acute distress, but complained of exertional dyspnea and frequent cough productive of blood-streaked sputum. On the fourth hospital day, while at rest, the patient had a sudden episode of hemoptysis which was associated with extreme dyspnea and cyanosis. He was immediately transferred to the Medical Service, where he was found to be stuporous and sweating profusely. Blood pressure was 120/90 mm. of Hg. Respirations were 36 per minute; the pulse rate was 130 per minute and regular. The lungs were full of coarse rhonchi, musical wheezes and moist râles. The heart sounds were heard with difficulty because of the respiratory noises. There appeared to be no murmurs present. No thrills or rubs were noted. For the next six days the patient continued to have episodes of hemoptysis and was almost always in a state of respiratory collapse, though there were some periods when the severity of the latter declined. He required oxygen constantly, and because of the tachycardia and pulmonary edema was digitalized. Since multiple pulmonary infarctions was one of the more likely diagnoses at the time of the first acute attack, anticoagulant therapy was started and continued for approximately three weeks.

On the tenth hospital day the hemoptysis stopped spontaneously and the respiratory distress gradually disappeared. At this time the lungs were clear to physical examination. The heart rate was normal and there were no murmurs. A markedly accentuated second sound was heard in the pulmonic area and in the fourth intercostal space to the left of the sternum. The patient's sensorium cleared; he was comfortable and no longer required oxygen. Several days later a rough, low-pitched systolic murmur was heard for the first time at the aortic area. This was transmitted throughout the entire right lung field as a loud systolic bruit. This murmur persisted without change during the remainder of the patient's life. Several studies were done during the asymptomatic period. Cardiac fluoroscopy revealed exaggeration of the pulmonary vascular markings in the hilar areas without hilar dance. There was enlargement of the pulmonary conus and of the adjacent pulmonary artery segment. Cardiac pulsations were normal. There was some suggestion of early right ventricular enlargement. None of the other chambers was involved. Tuberculin skin tests with first and second strength PPD were negative. The venous pressure in the right arm was 120 mm. of water. The arm-to-tongue circulation time (Decholin) was 14 seconds and the arm-to-lung time (ether) was 6 seconds.

During the following few weeks the patient remained relatively asymptomatic, but on three occasions attacks of acute pulmonary edema occurred which lasted for several hours and were quickly relieved by the administration of oxygen and sedation. On only one of these occasions was hemoptysis noted. With continued observation it became evident that a diagnosis of multiple pulmonary infarctions could not be substantiated. It also seemed quite clear that the patient's symptomatology could best

A



B

FIG. 2A. A coronal section of lungs and mediastinum. The infracarinal area is filled with dense connective tissue.
FIG. 2B. Diagrammatic representation of extent of pathologic involvement as seen in figure 2A.

be explained on the basis of increased pulmonary venous pressure. Since there was no objective evidence of congenital or rheumatic heart disease, an obstructive process involving either the left auricle or the pulmonary veins at some point close to their termination was postulated. Because of the prolonged nature of the illness, mediastinitis causing fibrous constriction of the pulmonary veins seemed most plausible. The diagnosis of myxoma of the left auricle was also considered. Since either of these conditions might be amenable to surgery, the thoracic surgeons were consulted. Bronchoscopy was suggested to rule out an intrabronchial lesion prior to other investigative procedures. During bronchoscopy, the patient suddenly experienced acute pulmonary edema. Blood rapidly welled up into the respiratory pas-

FIG. 2C. X-ray of postmortem specimen showing degree of calcification within the pathologic tissue.

sages, but no specific bleeding point could be identified. The bronchoscope was removed and the patient was returned to the ward. He failed to respond to treatment and died several hours later, on January 5, 1955. Permission for postmortem examination was obtained.

Pathologic Findings: The essential findings at autopsy were limited to the thorax. The viscera in the chest cavity were normally placed, and removal revealed a mass in the posterior mediastinum which measured 6.5 cm. by 5 cm. by 4 cm. The mass was centered in the infracarinal area between both major bronchi and was composed variously of pinkish tan, reddish brown, jet black and chalky yellow material. The mass completely replaced and obliterated the left and right inferior tracheobronchial lymph nodes and encased the pulmonary artery and vein at its bifurcation. These

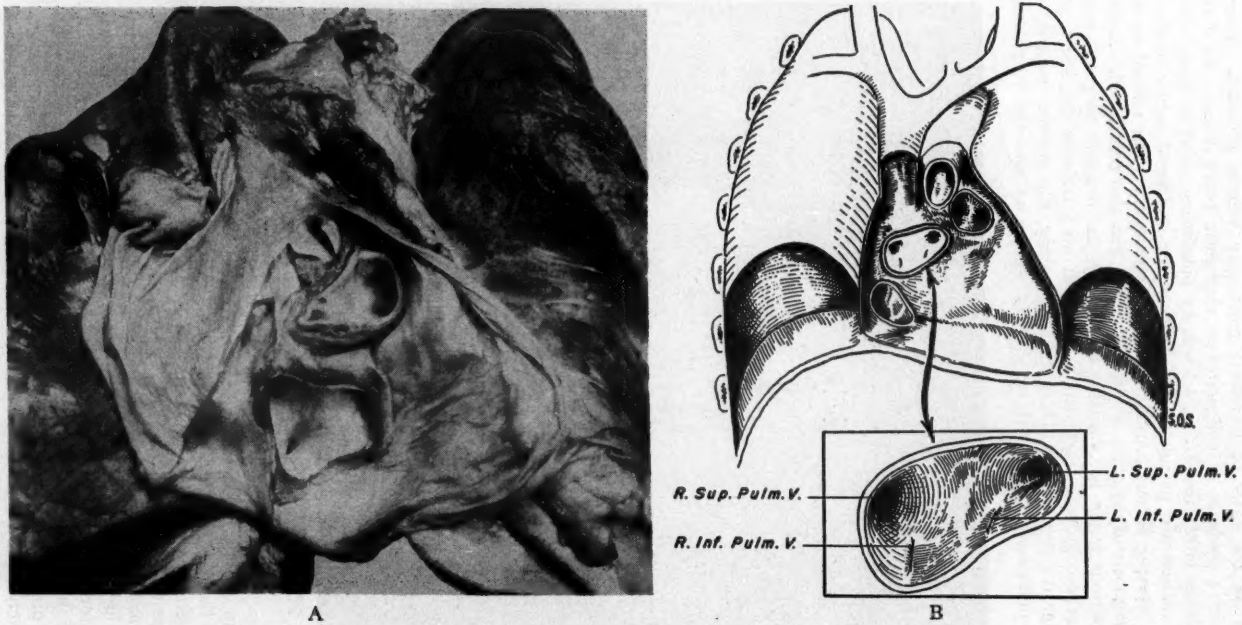


FIG. 3A. Ostia of pulmonary veins and arteries. Note marked narrowing of inferior pulmonary veins.
FIG. 3B. Diagrammatic representation of figure 3A.

vessels remained patent, but the right and left inferior pulmonary veins were completely stenosed as a result of constriction from without. The pulmonary veins from the upper lobes were not involved. Extensions from the mass were contiguous with and adherent to the posterior wall of the pericardial sac, a portion of the posterior surface of the superior vena cava, the mesial borders of the right and left lower lobe branch bronchi, and the esophagus (figures 2 and 3). The visceral and parietal pleurae over the lower lobes were adherent and contained irregularly dilated and tortuous vascular channels.

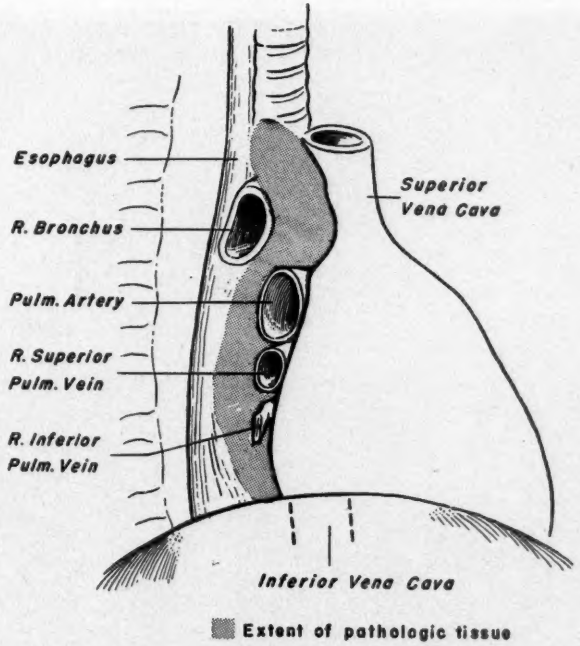


FIG. 3C. Artist's reconstruction of extent of pathologic involvement.

The lungs were increased in both volume and weight. Recent hemorrhages were present in focal areas in the lower lobes. There was evidence of chronic passive congestion and a bronchopneumonia.

The heart weighed 325 gm. and presented the classic findings of a cor pulmonale. The chambers on the right side were dilated and thickened, the wall of the right ventricle measuring 8 mm. in thickness. The heart valves were normal. The remainder of the viscera were not remarkable in appearance except for evidence of passive congestion. There was no sign of old perforation into the mediastinum from the tracheobronchial tree or esophagus.

The major and outstanding finding on microscopic examination of the mediastinal mass was dense fibrosis with collagenization, calcification and bone formation (figure 4A). In a few areas, rare foci containing lymphocytes, plasma cells, histiocytes and occasional giant cells of the Langhans and foreign body type were noted. In addition to the picture of chronic passive congestion and advanced, healing broncho-

pneumonia, the parenchyma of the lower lobes revealed an extensive sclerosis and muscular hypertrophy of the branches of the pulmonary artery and the pulmonary arterioles (figure 4C). These changes were striking in comparison with the minimal to moderate alterations in the vessels of the upper lobes. The bronchial submucosa distal to the point of obstruction of the pulmonary veins demonstrated the presence of a prominent ectasia and dilatation of venous and lymphatic channels. The adherent pleurae over the lower lobes contained numerous dilated vessels (figure 4B).

Special stains for the identification of tubercle bacilli (Ziehl-Neelsen), bacteria (methylene blue and Gram's stain) and fungi (periodic acid Schiff) were all negative.

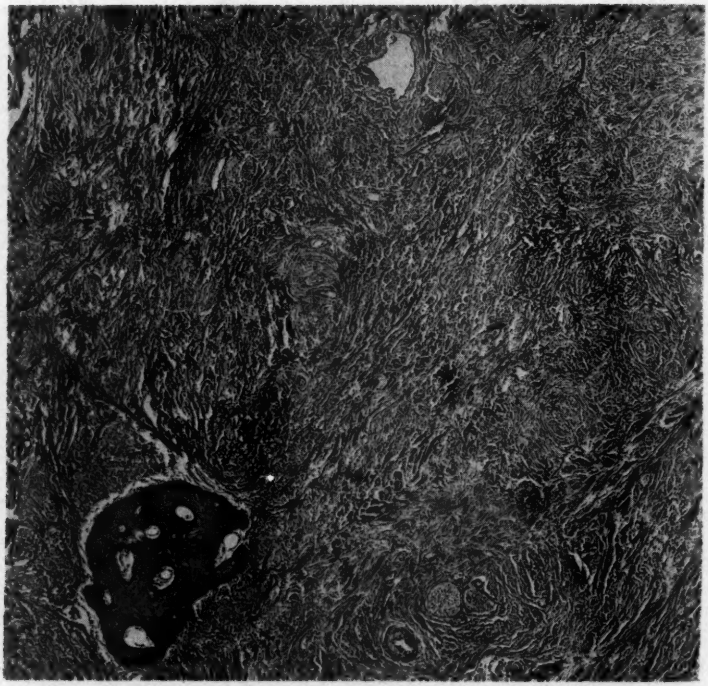


FIG. 4A. Microscopic section (25 dia.) of infracarinal mass.

In summary, the anatomic findings were those of an extensive, posterior mediastinitis involving primarily the pulmonary veins issuing from the lower lobes. The process appeared to be relatively old, with advanced healing seen in the form of collagenization and ossification. There were no specific pathologic features.

DISCUSSION

The Clinical Picture of Pulmonary Vein Stenosis: We have found reference to five cases of pulmonary vein stenosis in the medical literature.[3-6] Though some of these presentations are brief and do not include clinical details, a review of the major features of these cases and our own does allow a tentative composite picture to be drawn. Of the six patients, four were between the ages of 25 and

30, while the others were 35 and 42 and the ratio of men to women was four to two. At the time of hospitalization, the duration of symptoms in this group ranged from four to 10 years. In all of the patients dyspnea was a prominent symptom and cough was common. Hemoptysis was a striking manifestation in four of the cases. The paroxysmal nature of these symptoms was evident in the instances where details were available. The majority of the patients finally developed a picture of recurrent pulmonary edema or of intractable heart failure. Death resulted in all cases.

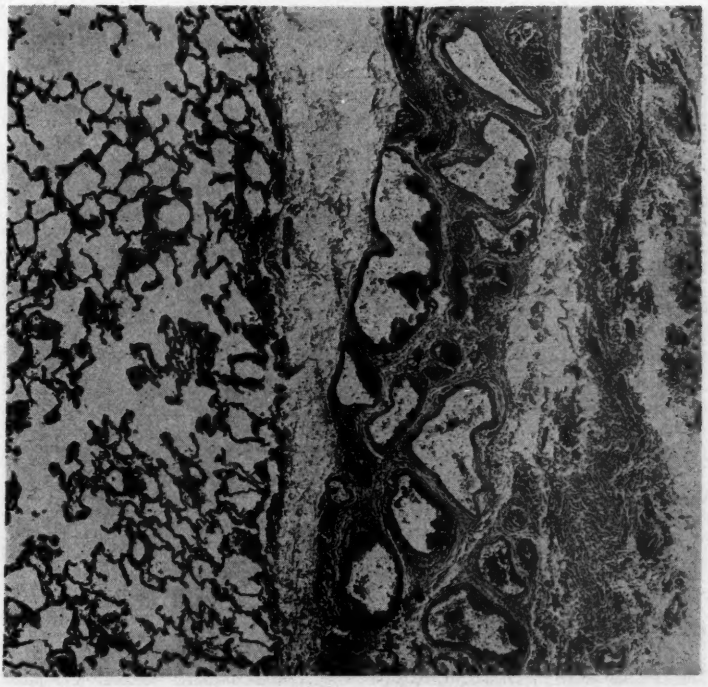


FIG. 4B. Microscopic section (29 dia.) of lung and pleura showing dilated vessels.

The physical and x-ray findings following occlusion of one or more pulmonary veins have had a definite pattern in the reviewed material. Pulmonary congestion and râles were noted in all cases. A loud second pulmonic sound and accentuated first apical sound were heard in five cases. Murmurs were heard in four but had no specific quality or location. The following murmurs were recorded: (1) apical systolic in two cases; (2) apical systolic and diastolic in one case; (3) loud systolic bruit throughout the right lung field in one case. X-ray of the chest typically revealed a mitral configuration, with varying degrees of cardiac enlargement and considerable enlargement of the pulmonary conus. Hilar vascular markings were usually increased. A definite mediastinal mass was noted in only one case. The electrocardiogram showed evidences of right ventricular strain.

Diagnosis and Differential Diagnosis: The antemortem diagnosis of pulmonary vein obstruction due to chronic mediastinitis is extremely difficult, since no specific pathognomonic signs exist. In general, a history of slowly progressive respiratory distress, with the subsequent development of the signs and symptoms of left heart failure, pulmonary hypertension and, finally, right heart failure in the absence of a definite picture of intracardiac disease, must lead the observer to a consideration of this condition. Careful probing of the past history for evidence of previous upper respiratory or pulmonary disease may be of assistance.

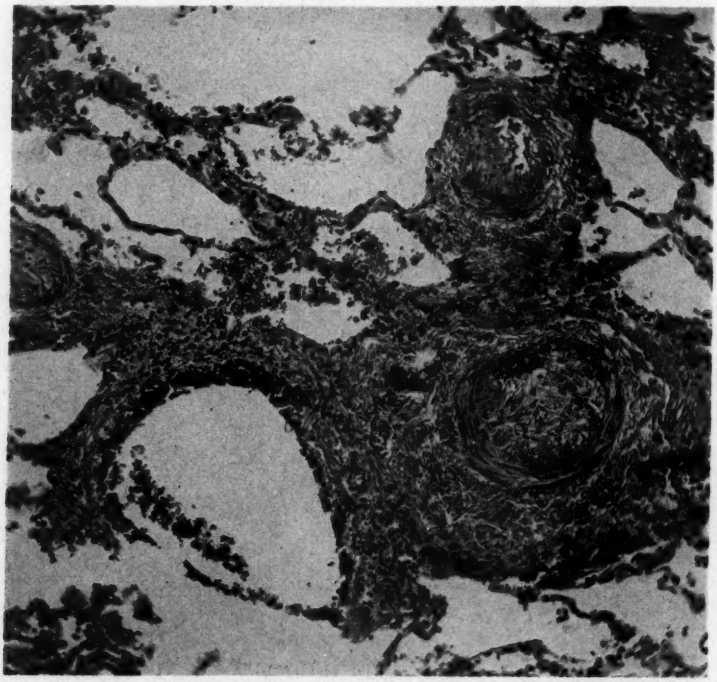


FIG. 4C. Microscopic section (150 dia.) of lower lobe showing extensive arteriolar changes.

The presence of murmurs or vascular bruits may be confusing, but it must be emphasized that these cannot be used as a means of excluding the possibility of these purely extracardiac lesions.

In the differential diagnosis one must deal primarily with mitral stenosis and tumors of the left auricle. This has been ably pointed out and discussed by Davis and Andrus,[3] who stress the advisability of x-ray kymographic studies, cardiac catheterization and angiocardiograms in doubtful cases, and point out that differentiation is not always possible by the usual clinical procedures. Though the need for such procedures in most cases is evident, caution must be exercised, for three of the six cases discussed above died following a stressful diagnostic procedure or surgical procedure. Primary and secondary tumors

involving the pulmonary veins [7-9] must on rare occasions be considered in the differential diagnosis.

Circulatory Dynamics: The major signs and symptoms of pulmonary vein obstruction are primarily the manifestations of pulmonary hypertension. The pathologic physiology is similar to that described in "pure" mitral stenosis.[10] Anatomically, the right ventricle hypertrophies and marked arteriosclerotic changes appear in the arterioles of those lobes affected by the venous obstruction. This latter process is minimal in the unobstructed lobes. The marked congestion of the unobstructed lobes may be explained, as suggested by Edwards and Burchell,[4] by the shunting of blood from areas of high pulmonary vascular resistance to these lobes in quantities exceeding the drainage potential of their normal venous channels.

The presence of a loud murmur in the absence of demonstrable valvular lesions, as described in our patient, has been reported by others.[1, 3, 4] No obvious explanation for the mechanism of this murmur is at hand, and it is not easily explained by the anatomic findings. One can broadly speculate on the possible relationship of these murmurs to the extensive collateral system built up in response to the pulmonary venous obstruction. However, no murmurs were heard in experimental animals (dogs) whose pulmonary veins were ligated and in whom considerable collateral circulation was developed.[11]

The vascular and tissue changes developing in response to pulmonary venous obstruction deserve special emphasis. For many years attempts have been made to produce such obstruction in animals, and excellent reviews of the history of this experimentation are available.[12, 13] Several important contributions have come from the work done to date. Hurwitz et al.[14] have conclusively demonstrated the extensive collateral circulation which develops in response to obliteration of the pulmonary veins. This collateral system consists primarily of the following three groups of vessels: (1) expanded bronchial collateral veins which communicate with major pulmonary veins by means of small, multiple connections and empty via hilar veins into intercostal or azygos veins; (2) transpleural hilar vessels which arise from the capillaries of granulation tissue in developing pleural adhesions, establish hilar connections with proximal ends of pulmonary veins, and drain into pericardiophrenic and occasionally branches of the superior intercostal, subclavian or brachial veins; (3) transpleural terminal veins which join end to end with distal ends of pulmonary veins, penetrate the pleura, and then drain into pericardiophrenic, intercostal and branches of the internal mammary veins. Functional observations [15] have indicated that these collaterals carry between 8 and 20% of the expected blood flow if venous drainage is intact. Though the postmortem material from our patient could not be examined by special technics, extensive collateral circulation was present which grossly confirmed the description above. This collateral circulation may have been responsible for the absence of any major degree of devitalization in the pulmonary tissues. The lungs showed primarily arteriolar changes, some resorbing hemorrhage and fibrosis. These findings in general are in agreement with those in animals surviving pulmonary vein ligation.[13, 16]

Etiology and Pathogenesis of Chronic Mediastinitis: Chronic mediastinitis was the responsible pathogenetic cause for the pulmonary vein obstruction in the cases thus far described. The etiology of this inflammatory process remains obscure. Observers have attributed such findings to syphilitic [17] and tuber-

culous [18, 19] involvement, without specific bacteriologic confirmation. The possibility of tularemic infection has been raised in a single case.[20] Several fairly clear-cut examples of mediastinitis secondary to trauma of the chest have been reported,[21, 22] and infection of the skin has also been suggested as a possible etiologic agent.[23] Tuberculosis, histoplasmosis and actinomycosis were found in three of 33 cases of chronic mediastinal lymphadenitis reported by Leech et al.,[5] but in the remaining 30 no specific etiology could be established. Another group of observers [24] has been content to call similar lesions nonspecific mediastinal granulomas, though struck by the resemblance to tuberculosis. Kunkel et al.,[25] in studying cystic and solid granulomatous lesions of the mediastinum, speculated on the possibility that these served as antecedents of an idiopathic constricting mediastinitis. Since careful bacteriologic examination for tubercle bacilli, Brucella and fungi failed to reveal evidence of specific organisms in their cases, the authors concluded that the cause of the lesions must be considered to be unknown. They also indicated that many of the cases previously reported as tuberculous in origin were based on tissue examinations with acid-fast staining technics, and that specific identification of *Mycobacterium tuberculosis* had not been made by strict bacteriologic standards.

In the patient whose case history we have presented, all of the clinical and histologic evidence appears to exclude the presence of the above mentioned agents, and the illness is presumed to have been precipitated by a bronchopneumonia at age seven. It is probable that low grade, smoldering, chronic inflammation may arise as a sequel to the ordinary respiratory infections which are seen in day-to-day medical practice through the pathway of mediastinal lymphadenitis. This concept of nonspecific upper respiratory infection as an important cause of chronic mediastinitis is not new, and was mentioned as early as 1887 in a paper presented by Hare,[1] and was stressed more recently by McIntire and Sykes.[26] In support of this concept, numerous reviews and case reports have appeared where mediastinal structures have been affected by a fibrous inflammatory mass which seemed causally related to antecedent, supposedly benign respiratory infection, or where such etiology was suggested by the absence of the signs and symptoms of specific infectious diseases.[3-6, 18-21, 25-29]

Chronic Mediastinitis—Clinical and Pathologic Findings: Chronic mediastinitis, indurative and fibrotic, is apparently the common end result of different etiologic processes. The localization of the process and the degree of compression of important structures determine the variety and intensity of the clinical pictures produced. For the most part, the literature has been preoccupied with the dramatic symptom complexes and has lost site of the common pathologic substrate.

Superior vena caval obstruction has received the greatest attention. McIntire and Sykes,[26] in reviewing 250 cases of this syndrome, found that 62 of these were due to chronic mediastinitis and that 25.8% of the latter appeared to be of the "idiopathic" or nonspecific variety. These figures are generally in agreement with those presented in other less extensive tabulations.[22, 30] Many individual cases of this type have been reported.[18-23, 26-28] Mixed pictures have also occurred, as evidenced by case 2 of Erganian and Wade,[20] where pulmonary artery, pulmonary vein and superior vena caval involvement was demonstrated at necropsy. The syndrome associated primarily with pulmonary vein occlusion is rare, but at least five cases in addition to ours have been noted in the litera-

ture,[3-6] and there is an indication that others are being prepared for publication.[3] Instances of chronic mediastinitis as a cause of tracheobronchial stenosis [25] and of pulmonary artery obstruction [31] have also been reported. Garamella [24] has presented examples of esophageal involvement. Lohman [29] has discussed several patients in whom the process appeared to be limited to the anterior mediastinum, with substernal and precordial pain as the prominent symptom. Inferior vena caval involvement might also be expected to occur, and a case of this type has been reported with plastic mediastinitis presumably due to tuberculosis.[32, 33] It may thus be seen that the events arising from specific structure involvement actually mirror those which might be predicted on an anatomic basis. Almost all of these structures have actually been found compromised by a mediastinal inflammatory process such as has been described in the foregoing pages. It must be emphasized that the striking nature of the symptomatic display has often led to a minimization of the basic pathologic lesion and a lack of appreciation of the importance of mediastinitis in differential diagnosis.

Summary

A case is presented of pulmonary vein obstruction arising as an uncommon sequel to nonspecific, chronic, fibrous mediastinitis. The close resemblance of the clinical picture produced by this condition to that of so-called "pure" mitral stenosis and to other lesions blocking the return of blood to the left side of the heart is stressed. The difficulty in establishing an antemortem diagnosis is discussed. Emphasis is placed on chronic, fibrous mediastinitis as the basic lesion in this case and others like it. It is pointed out that this lesion may produce a wide variety of symptom complexes as a result of involvement of other mediastinal structures. A characteristic lack of specificity is noted in the pathologic material, and the authors indicate that this fibrosis is probably the end result of different etiologic processes and pathogenetic mechanisms, among which may be the so-called benign upper respiratory infection.

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Summario in Interlingua

Chronic mediastinitis fibrose es un insidiose processo pathologic de origine obscur. Illo es probabilemente le resultato terminal de differente processos etiologic a mechanismos pathogenetic. Istos include possibilemente le si-appellate benigne infectiones supero-respiratori. Le morbo es characterisate per le deposition de un dense material collagenose e calcaree. Le presentia de un tal deposition produce pauc symptomas per se, sed illo pote resultar in le declaration de un extense varietate de dramatic complexos de symptomas que es manifestationes del disturbate patentia de importante structuras vascular in le mediastino. Le studios trovate in le litteratura esseva concernite primarimente con tal manifestationes secundari, specialmente le obstruction del vena cave. Obstruction del vena pulmonar es un sequella rar de iste disordine. Le characteristicas del syndrome vascular in question es discutite, e su similaritate pathophysiologic con stenosis mitral es signalate. Diagnose ante morte es possibile, ben

que le patientes non tolera ben le manovras diagnostic requirite. Il es a sperar que in le curso del tempore un solution therapeutic pro le problema de iste anormalitate mechanic va esser trovate in le forma de un intervention chirurgic.

Es reportate un caso del syndrome, occurrente in un masculo negre de 25 annos de etate qui primo notava dyspnea post exercitio e episodios de hemoptysis al etate de 22 annos durante un periode de servicio militar. Durante le intervallo, ille suffreva intermittente- sed progressivemente de dyspnea paroxysmal e sporadic episodios de hemoptysis. In le curso del ultime menses ante le hospitalisation, dyspnea, tusse, e hemoptysis se habeva intensificate. Le examine physic revelava forte grados de respiration stertorose in ambe pulmones. Le secunde sono plumonic esseva grandemente intensificate. Le electrocardiogramma significava deviation dextero-axial. Eveniva episodios de acute edema pulmonar. Oxygeno esseva necessari sin interruption. Le morte superveniva in acute edema pulmonar duo menses post le hospitalisation.

Le constatationes anatomic representava un extense mediastinitis posterior, afficiente principalmente le venas pulmonar originari del lobos inferior. Le processo esseva apparentemente ancian. Collagenisation e ossification esseva presente.

BIBLIOGRAPHY

1. Hare, H. A.: Pathology, clinical history and diagnosis of affections of the mediastinum, Fothergill Essay, 1889, P. Blakiston, Son and Company, Philadelphia.
2. Osler, W.: Principles and practices of medicine, revised by McCrae, T. M., 1927, D. Appleton and Company, New York.
3. Davis, F. W., Jr., and Andrus, E. C.: Mitral stenosis in facsimile, New England J. Med. **251**: 297, 1954.
4. Edwards, J. E., and Burchell, H. E.: Multilobar pulmonary venous obstruction with pulmonary hypertension, Arch. Int. Med. **87**: 372, 1951.
5. Leech, T. R., Meckstroth, C. V., and Klassen, K. P.: Exploratory thoracotomy in chronic lymphadenitis of the mediastinum, Arch. Surg. **71**: 383, 1955.
6. Heggelin, R., and Zollinger, H.: A case of pulmonary sclerosis of particular etiology (scar tissue of the mediastinum), Cardiologia **24**: 92, 1954.
7. Kaplan, S.: Leiomyofibroma of left pulmonary vein invading pericardium in child 3½ years old, Rev. franç. de pédiat. **10**: 664, 1934.
8. Ravid, J. M., and Sachs, J.: Tumors of heart with report of primary fibromyxosarcoma of left auricle and pulmonary vein, associated with multiple tumors of mesentery and alimentary tract, Am. Heart J. **26**: 385, 1943.
9. McDonald, S., Jr., and Heather, J. C.: Neoplastic invasion of pulmonary veins and left auricle, J. Path. and Bact. **48**: 533, 1939.
10. Dexter, L.: Pathologic physiology of mitral stenosis and its surgical implications, Bull. New York Acad. Med. **28**: 90, 1952.
11. Calabresi, M.: Personal communication.
12. Birnbaum, G. L.: Anatomy of the bronchovascular system, 1954, The Year Book Publishers, Inc., Chicago.
13. Swan, H., and Mulligan, R. M.: Experimental study of effect of ligation of pulmonary vein in dog, J. Thoracic Surg. **17**: 44, 1948.
14. Hurwitz, A., Calabresi, M., Cooke, R. W., and Liebow, A. A.: An experimental study of venous collateral circulation of the lungs. I. Anatomical observations, Am. J. Path. **30**: 1085, 1954.
15. Hurwitz, A., Calabresi, M., Cooke, R. W., and Liebow, A. A.: An experimental study of venous collateral circulation of the lungs. II. Functional observations, J. Thoracic Surg. **28**: 241, 1954.
16. Wyatt, J. R., Burke, D. R., and Hanlon, C. R.: Morphologic study of canine lungs after ligation of pulmonary veins, Am. J. Path. **29**: 291, 1953.

17. Knox, L. C.: Chronic mediastinitis, Am. J. M. Sc. **169**: 807, 1925.
18. Pilcher, L. S., and Overholt, R. H.: Venous obstruction in the upper mediastinum, Ann. Surg. **100**: 74, 1934.
19. Hinshaw, H. C., and Rutledge, D. I.: Lesions in the mediastinum which interfere with venous circulation, J. Lab. and Clin. Med. **27**: 908, 1942.
20. Erganian, J., and Wade, L. V.: Chronic fibrous mediastinitis with obstruction of the superior vena cava, J. Thoracic Surg. **12**: 275, 1945.
21. Gray, H. K., and Skinner, I. C.: Constrictive occlusion of the superior vena cava, 3 cases treated surgically, Surg., Gynec. and Obst. **72**: 923, 1941.
22. Ochsner, A., and Dixon, J. L.: Superior vena caval thrombosis, J. Thoracic Surg. **5**: 641, 1936.
23. Rose, L. B.: Obstruction of the superior vena cava of 25 years' duration, J. A. M. A. **150**: 1198, 1952.
24. Garamella, J. J., Stutzman, F. L., Varco, R. L., and Jensen, N. K.: Subcarinal mediastinal granulomas causing esophageal obstruction, J. Thoracic Surg. **30**: 187 (Aug.) 1955.
25. Kunkel, W. M., Jr., Claggett, O. T., and McDonald, J. R.: Mediastinal granulomas, J. Thoracic Surg. **27**: 565, 1954.
26. McIntire, F. T., and Sykes, E. M., Jr.: Obstruction of the superior vena cava: a review of the literature and report of two personal cases, Ann. Int. Med. **30**: 925, 1949.
27. Rutledge, D. I., and Gray, H. K.: Indeterminate type of obstruction of superior vena cava, Proc. Staff Meet., Mayo Clin. **14**: 337, 1939.
28. McCord, M. C., Edlin, P., and Block, M.: Superior vena caval obstruction, Dis. of Chest **19**: 19, 1951.
29. Lohman, A. J. M.: Mediastinitis anterior chronica, Acta med. Scandinav. **131**: 51, 1948.
30. Hinshaw, D. B.: Obstructions of the superior vena cava, Am. Heart J. **37**: 958, 1949.
31. Söderberg, G.: On striktur av arteria pulmonalis genom skrumpuunde mediastinit, Nord. med. **28**: 2051, 1945.
32. Amorim, A.: Mediastinite plástica e síndrome de compressão cava inferior, Rev. brasil. de cir. **12**: 405, 1943.
33. Amorim, A.: Mediastinite plástica e síndrome de compressão cava inferior, Laudo parcial de necrópsia, Bol. Col. di brasil cirurgiões **18**: 225–228 (July) 1943.

MUSSEL POISONING*

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Poisoning from shellfish has become a little known clinical entity in this country except in certain of the coastal areas, where sporadic cases appear. Not too many years ago it occurred occasionally in epidemic proportions, as in California in 1927,[1] but more recently it has been observed so infrequently that many persons have relegated it to the status of a myth or "old wives' tale." This form of food poisoning is seen most often on the Pacific Coast of this continent, but cases are reported from the Nova Scotia area, northern Europe and South Africa.

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Many of the details were first reported in the medical literature of the last century and, as might be expected, the case descriptions are vivid.[2, 3, 4, 5, 6] Since current medical literature is rather devoid of clinical data on this disease, it seemed worth while to detail the clinical courses of two cases observed in California in 1954.

Case Reports

Case 1. H. F., a 27 year old white Air Force sergeant, and his 23 year old wife, C. F. (case 2), spent the day of August 29 digging mussels along a beach on the Marin County coast, a short distance north of the Golden Gate. Although this area is posted to warn against the ingestion of potentially poisonous shellfish from May 1 to October 31, this couple did not notice the warnings. They were aware of a dangerous season for bivalves but reasoned that September, containing the letter "R" in the spelling, was three days hence, giving them an adequate margin of safety.

The mussels were stored on ice until the following evening, when they were steamed and eaten at approximately 8:00 p.m. One hour later, the husband noticed a gradual onset of numbness and tingling in the fingertips and lips. At about 10:00 p.m. his wife noticed similar sensations. Both felt well, however, and went to bed for the night a short while later.

The husband awoke at approximately 2:00 a.m. and was aware of marked dizziness and a "floating sensation." The numbness and tingling were still present in fingertips and lips and had progressed to the circumoral area and the legs. He awakened his wife, but she was unable even to sit on the edge of the bed because of lack of equilibrium. She described this sensation as a "feeling of floating" or of being "very drunk," but did not experience actual vertigo. Her touch sensation was diminished, but her hearing and vision were unimpaired. When she attempted to run to the bathroom she fell after a few steps but did not injure herself. Her husband also walked with great difficulty but was able to assist her into bed and then walk a short distance to a neighbor's house for aid. By telephone, a physician advised a tap water enema and one third glass of an oral saline cathartic, which were administered to the wife but not taken by the husband. Within a few minutes she began vomiting stomach contents containing large quantities of mussels. Diarrhea, profuse in quantity, began shortly thereafter and continued for several hours. There was no incontinence of urine and feces, and vomiting did not continue. She had no seizures and did not complain of headache. The husband dozed for several hours and noticed less dizziness on awakening. He drove to his Air Force unit and was admitted to the Medical Ward of Beale Air Force Hospital at 10:00 a.m. on August 31. Arrangements had been made for his wife to be brought by ambulance and admitted at the same time.

On admission the husband complained only of giddiness, lightheadedness, and numbness and tingling of the lips, fingertips and lower extremities below the knees. There had been no nausea, vomiting or bowel movements after the onset of symptoms. Physical examination revealed an oral temperature of 98.6° F., blood pressure of 130/90, pulse rate of 86 per minute, and respirations of 16 per minute. There was a hesitant, lisping speech, with slurring of words not obvious to the patient. General physical examination was essentially negative, although a pronounced apical systolic thrust was noted. Neurologic examination showed the following abnormal findings: slurred speech; generalized decrease in sensation to pinprick; generalized muscle weakness, equal bilaterally; generalized decreased touch sensation, especially marked but equal bilaterally in hypothenar eminences and fingertips; diminished vibratory sensation at the medial malleoli and metatarsals; generally normal finger-to-nose test with eyes open, but grossly abnormal with eyes closed; markedly positive Romberg's,

but some swaying with eyes open. Treatment was through supportive measures, and he was administered 2,000 ml. of 5% glucose in water with 10 ml. aminophylline intravenously. A soap-water enema produced a normal stool, and gastric tube aspiration brought out 50 ml. of mucus and thin yellow fluid with no solid particles. This patient remained in bed and dozed intermittently throughout the day. On the following morning he felt stronger and complained only of numbness and tingling in the fingertips and lips. Neurologic examination revealed diminished touch and pinprick sensation only in the hypothenar eminences and fingertips. The Romberg test and finger-to-nose tests were normal. His speech was distinct. Lumbar puncture performed at this time revealed a recumbent pressure of 254 mm. H_2O, but 130 mm. after relaxation. The fluid was clear and colorless, containing 19 white blood cells (all lymphocytes) and 15 red blood cells. Spinal fluid chemistry and bacteriologic studies were negative. Twenty-four hours later only slight numbness of the fingertips persisted, and on the following day he was completely asymptomatic. Electrocardiograms on the day of admission and three days later were within normal limits. Complete blood counts and urinalyses were normal.

Case 2. C. F., on admission, was noted to be lying quietly in bed, able to speak only with great effort, and unable to move the extremities to any extent. There was no obvious dehydration or respiratory embarrassment. The temperature was 99.0° F. orally, pulse rate 86 per minute and regular, blood pressure 110/78 and respirations 24 per minute but irregular. The skin was cool and moist. There was marked suprapubic tenderness, but no fullness in this region. Menstruation had begun the previous evening. Neurologic examination revealed the following abnormal findings: dysarthria; marked weakness of all peripheral muscle groups, equal bilaterally; inability to sit because of marked subjective vertigo; diminished sensation to touch and pinprick in all areas. Deep pain sensation and vibratory sensation were intact. All cranial nerves showed normal function. Reflexes were active but normal, and there were no pathologic reflexes.

Following her admission this woman was observed closely. Respirations persisted at 24 to 26 per minute but remained irregular and often resembled Cheyne-Stokes breathing. She complained of occasional severe, fleeting, cramping pains in both arms, not extending to shoulders or forearms. A tracheotomy set, machine aspirator, and respirator were kept nearby at all times. Her clinical course during this day is chronologically detailed below:

At 11:00 a.m., one hour after admission, she complained of severe spasmodic suprapubic pain and urinary urgency but inability to void. Catheterization relieved these symptoms temporarily and withdrew a small amount of urine. Urinalysis revealed a pH of 4, specific gravity of 1.010, negative albumin and sugar, and 1 to 2 white blood cells per high power field.

At 12:00 noon she was started on intravenous feedings, 1,000 ml. of 5% glucose in water. Atropine therapy was begun, gr. 1/200, to be given every four hours subcutaneously.

By 1:00 p.m. she had developed continual bladder spasm, with much suprapubic pain and tenderness. There was a marked exacerbation of emotional responses, and she cried fitfully when catheterization was attempted or the intravenous restarted. During this hour she began to complain of occasional dull cramping precordial pain, not radiating, and without change in heart rate, sounds or rhythm. Muscle weakness progressed. Laboratory studies showed a white blood count of 11,200, with 78% neutrophils and 22% lymphocytes. The hemoglobin was 15 gm.

At about 2:00 p.m. she began vomiting, although she had been given nothing by mouth. During this episode she had marked respiratory difficulty, with shallow, irregular respirations and slight cyanosis for five to 10 second periods, despite manual artificial respiratory aid. There was no coughing or choking to indicate aspiration

of vomitus, which consisted of mucus and food particles. Passage of a stomach tube was forcefully resisted by the patient. A high tap-water enema was not productive of much fecal matter.

At 3:00 p.m. a Levine tube was passed successfully and continuous suction applied, although vomiting had not recurred. Within the next hour, 150 to 200 ml. clear fluid and mucus were withdrawn, but the patient continued to complain of irritation and nausea caused by the tube. A second 1,000 ml. of 5% glucose in water was started intravenously.

At about 5:00 p.m. she began to complain again of suprapubic pain and tenderness, and an indwelling catheter was successfully inserted, with rapid relief of symptoms. She again noticed intermittent pains in both arms, now extending into the forearms. Neurologic examination was essentially unchanged. An electrocardiogram showed a sinus arrhythmia, with an average ventricular rate of 83 per minute, normal PR, QRS and QT intervals, flat T-waves in AVF and V_2, and inverted T-waves in III, V_1, V_3 and V_4.

By 8:00 p.m. she was quieter and resting well. Breathing was deeper and more regular, and there were no complaints of pain. There was no vomiting after removal of the Levine tube. One thousand milliliters of 5% glucose in saline with 2 gm. of potassium chloride were given intravenously. During the remainder of the night she rested quietly.

On the following morning, September 1, she felt improved and had regained much of her muscle power, but retained the numbness and tingling sensations in fingertips and lips. Physical examination still revealed swaying with the patient standing with eyes open or closed, and there was hypersensitivity of the fingertips to touch and pinprick not found in the circumoral area or lips. The indwelling catheter was removed. She tolerated oral fluids well, but was retained on atropine medication. Electrocardiograms were unchanged, except that the T-wave in V_2 was now upright.

On September 2 she was able to walk short distances in her room but could not climb back into bed because of muscle weakness. There no longer was any complaint of dizziness or lightheadedness, and numbness and tingling in lips and fingertips had disappeared. Urgency of urination was present, along with some frequency and nocturia. She continued to tolerate oral fluids well. Electrocardiograms on this date showed T-wave inversion in III and precordial Leads V_1 through V_4, with flat T-waves in V_5 and AVF.

During her fourth hospital day, September 3, she was noted to be gaining strength gradually and tolerating a progressive diet. However, a marked personality change was noted in that she became withdrawn and resentful, uncoöperative during the necessary laboratory studies, and abusive toward the ward personnel. Only repeated persuasion by her husband and physicians prevented her from leaving the hospital. Whether this represented part of her illness or a reflection of her usual personality structure could not be determined, since she had not been interviewed in any of the hospital clinics prior to her illness. Her relations with hospital personnel remained in this state until her release from the hospital on September 7. She had gradually regained strength and was free of urinary symptoms. By this date the electrocardiogram had shown definite changes, with T-waves diphasic in III, upright in AVF, V_2, V_4, V_5 and V_6, and inverted only in V_1 and V_3. Throughout her hospital course she had remained afebrile. The pulse rate was regular and did not rise above 94 per minute. Respirations varied between 14 and 24 per minute, with the exception of the period of respiratory difficulty on the day of admission. The blood pressure remained within normal ranges. Repeated blood counts were normal, and the blood serology was negative. Urinalyses continued to show a strongly acid urine, pH 4, with cellular contents indicating menstruation. Spinal tap was not done.

Discussion

Poisoning from bivalves follows ingestion of a heat-stable toxin. The origin of the toxin is not the shellfish itself but has been traced back to reveal a fascinating account of transfer from lower to higher organism. From the studies of Sommer and others [7] it is known to be produced by and liberated from the dinoflagellate plankton, *Gonyaulax catenella,* which is abundant along certain coastal areas during the summer season. This toxin is absorbed by the adjacent bivalves which filter out and feed on the plankton, the dark digestive organ taking up the toxin in high concentrations, while the muscle portion is less affected. Although all bivalves which feed on plankton are potentially poisonous, those which reach dangerous levels of toxicity are mussels and clams. Humans ingest large quantities of the toxin only by eating the entire body of the mussel or clam, including the viscera. Steaming or boiling does not destroy the toxin, but the addition of an alkali such as sodium bicarbonate will reduce the potency somewhat.

This toxic agent is known to be an alkaloid with muscarine-like actions. It is a potent neurotoxin,[8] and the clinical syndrome produced is essentially one of progressive nervous involvement. Initial symptoms may occur within one hour after the meal, signaled by tingling about the lips and in fingers and toes, rapidly progressing to legs and forearms. Within a few hours there is paralysis of the extremities, often with diminution of sensation or complete anesthesia of these areas. Vertigo is common, but most often a floating sensation or a feeling of being "very drunk" is described. There is incoherence of speech and occasionally complete aphasia. Paralysis becomes progressive, extending to the neck and muscles of respiration, making artificial aid to breathing necessary in the severe cases. Most patients are calm, but mental excitement has been reported in two cases [6] and was prominent in the clinical course of case 2. Reflexes usually are not affected. Convulsive seizures have been reported but are uncommon.[4] Gastrointestinal symptoms are rare except in the very severe cases. Abdominal pain is also rare, but was noted to be a prominent factor associated with urinary bladder spasm in case 2. Vision usually is not affected, but temporary blindness has been reported in one case.[5] Survival beyond 12 hours from the onset of symptoms is a good prognostic sign, and recovery is gradual, with numbness and tingling of the extremities the last symptoms to disappear.

Pharmacologic studies have shown that this toxin has both central and peripheral actions, with the peripheral effects predominantly on the ganglion cells of the medulla and the large nerve cells in the ventral horn of the spinal cord.[9] The central action occurs in the respiratory and cardiovascular centers.[8] It is a more potent depressor of respiration, in that experimental animals whose respirations have ceased continue to show regular cardiac action for short periods.[10] Prinzmetal has shown further that there is little total effect on blood pressure and heart rate in dogs, even with large doses, and this minimal effect most likely is mediated through central action. A direct action on the myocardium has not been evaluated thoroughly, although varying degrees of heart block have been observed.[10] The electrocardiographic changes in case 2 are of interest, since they show T-wave changes which would suggest a direct action of the toxin on the myocardium. No conduction defect was observed. (Unfortunately, the tracings were technically not satisfactory for reproduction.) Although other toxins may have been ingested with the mussels, this finding bears

further investigation and suggests that the toxin may act directly on the myocardium as well as on nervous tissue.

There is an individual variation in response to the toxin, but it has been determined that for susceptible persons, mild symptoms occur only when 2,000 or more mouse units have been ingested. Severe symptoms occur from over 10,000 units. A total of 60 empty pairs of mussel shells was counted from the home of the patients reported here. From samples of unconsumed mussels, analyses were made by the California State Public Health Department and revealed a level of 1,246 mouse units per 50 gm. of tissue. This would indicate that each consumed in excess of 15,000 mouse units of toxin.

Much has been done by state public health departments to reduce the incidence of this intoxication. Warning signs have been posted along the Pacific Coast to indicate that the dangerous season is from May 1 to October 31, since all cases have fallen within this period. The patients discussed here represent two of the five cases reported in California in 1954. None was reported in that state during the preceding five years. Effective methods of public information have apparently dispelled many of the misconceptions held by the public concerning this illness in "endemic" areas. Government inspection has been in force for many years and has been effective in insuring the safety of commercially available shellfish.

Summary

Two cases of poisoning from ingested mussels are reported, one with apparent myocardial involvement.

Summario in Interlingua

Invenenamento per testaceos es un pauco cognoscite entitate clinic, excepte in certe areas costal ubi casos de illo occurre sporadicamente. Le agente etiologic es un toxina de character thermostabile que es liberate per le dinoflagellate plancton *Gonyaulax catenella*. Durante le saison calide, isto pote abundar in tal areas. Le toxina es absorbite per bivalvos que se nutri de plancton. Lor organos digestive absorbe alte concentrationes durante que le portion muscular es afficite minus pronunciatemente. Post su ingestion per humanos, le agente deveni un potente neurotoxina con action central in le centros respiratori e cardiovascular e action peripheric in le cellulas ganglionic del medulla e le grande cellulas in le corno ventral del cordon spinal.

Clinicamente le syndrome es characterisate per un affection progressive del nervos. Es reportate duo casos. In ambes, mytilos ab le costa septentrional de California habeva essite ingerite. Ambes occurreva verso le fin de augusto 1954. Un del patientes habeva leve symptomas de vertigine con torpiditate e formication in le extremitates e le area circumoral. Le secunde patiente disveloppava marcate grados de vertigine, debilitate de omne gruppos peripheric de musculos, e reducite sensibilitate a contacto e aguliation in omne areas. Durante le prime die illa exhibiva marcate grados de dolorose spasmos del vesica urinari e embarasso respiratori que requireva le adjuta de respiration artificial. Electrocardiogrammas in iste caso revelava nulle obvie defecto conductional sed alterationes del undas T in le derivationes III, AVF, e V_{1-5}. Quando le patiente esseva dimittite ab le hospital, ille anormalitates habeva disparite essentialmente. Isto pareva indicar que le toxina exerce possibilemente un action directe super le myocardio. Le analyses de mytilos non-ingerite monstrava que le patientes habeva consumite (individualmente) plus que 15.000 unitates-mus de toxina. Isto excede per multo le minimo de 10.000 unitates que es usualmente requirite pro producer symptomas sever.

BIBLIOGRAPHY

1. Meyer, K. F., Sommer, H., and Schoenholz, P.: Mussel poisoning, J. Prev. Med. 2: 365, 1928.
2. Permewan, W.: A fatal case of poisoning by mussels, with remarks on the action of the poison, Lancet 2: 568, 1888.
3. Anderton, C.: Poisoning by mussels, Brit. M. J. 1: 500, 1882.
4. Farrar, J.: Case of mussel poisoning: recovery, Brit. M. J. 1: 939, 1882.
5. Todd, G. B.: Case report, Brit. M. J. 2: 749, 1891.
6. Rolfe, R.: Two cases of poisoning by mussels—one fatal, Lancet 2: 593, 1904.
7. Sommer, H., Whedon, W. F., Kofoid, C. A., and Stohler, R.: Relation of paralytic shell-fish poison to certain plankton organisms of the genus *Gonyaulax*, Arch. Path. 24: 537, 1937.
8. Kellaway, C. H.: The action of mussel poison on the nervous system, Australian J. Exper. Biol. and M. Sc. 13: 79, 1935.
9. Covell, W. P., and Whedon, W. F.: Effects of the paralytic shell-fish poison on nerve cells, Arch. Path. 24: 411, 1937.
10. Prinzmetal, M., Sommer, H., and Leake, C. D.: The pharmacological action of "mussel poison," J. Pharmacol. and Exper. Therap. 46: 63, 1932.

PULSATING METASTASIS OF THE FEMUR FROM A SILENT HYPERNEPHROMA *

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A SOLITARY pulsating tumor of bone is a rare occurrence. It is important clinically in that it usually represents a metastasis from a carcinoma of the kidney or thyroid.[1] The primary tumor itself may be entirely asymptomatic.

According to Willis,[1] the first case of pulsating metastases was described by Morris [2] in 1880. The patient was observed for six years, during which time she developed pulsating tumors in the parietal bone, the clavicle and both hips. At autopsy, the metastatic lesions had the colloid vesicular structure of thyroid carcinoma. Since then additional cases have been reported sporadically in the medical literature.[3-14] Pulsating metastases situated in bones adjacent to major arteries have been mistaken in the past for aneurysms. When the sternum is involved an aneurysm of the ascending aorta may be misdiagnosed.[3, 4, 5, 6] Bullowa [7] described a pulsating mass destroying the lower dorsal spine which was thought to be an aneurysm of the descending aorta. Metastasis to the femur can give the appearance of an aneurysm of the femoral artery.[8, 9] In one case in which the clavicle was the site of metastasis, a subclavian artery aneurysm was originally suspected.[9] Such problems in diagnosis need not exist today. The destructive lesion in the bone can be visualized readily on x-ray examination. In a few cases, angiography will help to establish the diagnosis.

We are reporting a case of pulsating metastasis in the femur from a silent hypernephroma to reëmphasize this unusual physical finding and to illustrate the radiographic visualization of the aneurysmal nature of the tumor by injecting Diodrast into the femoral artery.

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Case Report

A 56 year old male was admitted for the second time to Beth Israel Hospital on September 24, 1954. For four months he had had pain in the right leg, and for three months progressively increasing pain in the right hip. His first admission was in 1946 for painful hematuria due to a ureteral calculus. Diabetes mellitus was diagnosed in 1950. Intermittent claudication and angina of effort appeared in 1953.

Physical examination on admission revealed an obese white male. Optic fundi showed grade I hypertensive retinopathy. The thyroid gland was not enlarged. The lungs were clear. The heart was not enlarged, the sounds were of good quality and the rhythm was regular. Pulse rate was 80/min.; A_2 was greater than P_2; blood pressure, 160/90 mm. of Hg. The abdomen was free from masses. The prostate was moderately enlarged and smooth. Marked tenderness was elicited by palpation over the right greater trochanter, and by rotation of the right thigh. Straight leg raising was normal bilaterally.

Laboratory tests gave the following results: hemoglobin, 13.0 gm.; white blood count, 10,450; polymorphonuclears, 48%; stab, 2%; lymphocytes, 42%; eosinophils, 6%; monocytes, 2%. Urine specific gravity, 1.018; albumin, negative; glucose, negative; acetone, negative; microscopic sediment, negative. Fasting blood sugar, 116 mg.%; nonprotein nitrogen, 38 mg.%; bilirubin, 0.88 mg.%; bromsulfalein, less than 5% retained after 30 minutes; alkaline phosphatase, 5.3 Bodansky units; acid phosphatase, 0.32 Bodansky units; calcium, 10.5 mg.%; phosphorus, 3.2 mg.%. Wassermann, Mazzini and Kahn tests, negative. Bone marrow examination was normal.

X-rays of the right hip revealed a large osteolytic defect involving the right femur in the region of the greater trochanter and the adjacent neck and shaft. The cortex was destroyed and the mass extended into the adjacent soft tissues (figure 1A). Radiographic examination of the rest of the skeletal system did not disclose any other bony abnormalities. Chest x-ray showed normal lungs.

The clinical and radiographic impression on admission was that of a solitary metastatic carcinoma from a latent primary source. On the patient's second day in the hospital the right hip was reëxamined. A distinct mass could be felt in the region of the greater trochanter. It was tense but fluctuant, and had a definite systolic pulsation. A loud systolic bruit could be heard over it. Compression of the right femoral artery just distal to the inguinal ligament caused immediate disappearance of the pulsation and bruit and considerable reduction in size of the mass. There was no slowing of the pulse rate during this maneuver (negative Branham's reflex).

The solitary pulsating metastasis and a grossly normal thyroid suggested the likelihood of an asymptomatic renal carcinoma. An intravenous pyelogram confirmed this suspicion. The left kidney was large. The pelvis appeared to be depressed by a mass which also elongated and depressed the upper calyx and displaced the upper portion of the left ureter. The right urinary tract was normal. The prostate was enlarged. A left retrograde pyelogram substantiated the presence of a tumor mass in the upper pole of the left kidney.

An attempt was made to visualize the aneurysmal nature of the metastasis. Twenty-five cubic centimeters of 35% Diodrast were rapidly injected into the right femoral artery while the artery distal to the needle was occluded with a blood pressure cuff. The femoral artery and its branches were well visualized. The tumor was immediately opacified (figure 1B).

Left nephrectomy was performed on October 14, 1954. At operation a mass in the upper pole of the left kidney was found, and a large amount of inflammatory reaction around the pelvis and capsule of the kidney. Gross pathologic examination of the specimen revealed a 5 cm. mass arising from the posterior surface of the kidney in its midportion. It extended forward and into the upper pole of the kidney.

There was no tumor invasion of the pelvis or renal vein. Microscopic examination disclosed a clear cell carcinoma of the kidney with areas of necrosis.

The postoperative course was uneventful. The patient remained bedridden because of severe pain in the right hip. Radiation therapy of 15,000 r was given in divided doses through a grid. The pain decreased but there was no diminution in the size of the mass or alteration of its pulsation or bruit. The patient was gradually mobilized with the aid of a hip brace and crutches, and was discharged on December 18, 1954.

A B

FIG. 1. A. Large osteolytic lesion involving the greater trochanter and the adjacent neck and shaft of the right femur. B. The aneurysmal nature of the metastasis and its extension into the soft tissues are immediately visualized by Diodrast injected into the femoral artery.

He was re-admitted on January 12, 1955, because of the development of pain in the left hip and lumbar area. X-ray films of the lumbosacral spine revealed almost complete destruction of the body of L 3. No pulsation was felt over the area. The metastatic lesion in the right femur had grown in size and still pulsated. Fourteen thousand roentgens were given to the lumbar spine through a grid, with some relief of pain. The patient was discharged to a nursing home. He died with widespread metastases on May 11, 1955, eight months after his first admission and one year after his first symptom. Autopsy was not obtained.

DISCUSSION

Osteolytic metastatic lesions usually arise from carcinoma of the breast, thyroid, kidney, lung or prostate. Pulsation in such a bone lesion narrows the sites of origin to either the thyroid or the kidney. In the case reported the thyroid was grossly normal. In spite of the normal urine examination and the absence of any abnormal renal signs or symptoms, a primary carcinoma of the kidney was suspected. Intravenous pyelography confirmed this clinical diagnosis.

The outstanding pathologic feature of a pulsating metastasis is its vascularity and the free communication of its vascular spaces with its arterial supply. The tumor tissue constitutes a small part of the total mass. Cell necrosis takes place, leaving a shell of flat cells lining large vascular spaces. In the past, metastases have been removed in such cases and mistakenly diagnosed as endotheliomas.[1] In Bullowa's case small lobules of tumor tissue were found dangling in wide blood channels.[7]

The aneurysmal nature of the metastasis in our case was strikingly demonstrated by Diodrast injected into the femoral artery. The tumor was instantly opacified to a density almost equal to that of the normal bone and the femoral artery (figure 1). Also visualized was a substantial extension of the tumor into the soft tissues around the hip and the shaft of the femur.

Pulsating bone metastases from carcinoma of the kidney or thyroid may be solitary or multiple. Solitary ones may be associated with nonpulsatile metastases in other bones. This was so in the case described here, as well as in others in the literature. The development of pulsation probably depends in large measure upon the nature of the local blood supply to each metastasis. Those that establish a communication with a large nutrient artery or with several branches of a nutrient artery will pulsate.

Pulsating metastases present the classic signs of aneurysm. A systolic expansile pulsation and a systolic thrill and bruit are present in every case. In no instance were the signs of an arteriovenous aneurysm found. Our case afforded an opportunity to test for the Branham reflex. Occlusion of the femoral artery caused disappearance of the pulsation in the tumor, but there was no slowing of the pulse, as occurs when an arteriovenous aneurysm is obliterated.

The diagnosis of pulsation in a bone tumor is of more than academic interest. It is important in reaching an accurate differential diagnosis. Most commonly, it indicates a metastasis from a primary carcinoma of the kidney or thyroid. The primary tumor in the thyroid may be small but detectable by careful clinical examination. However, the primary tumor in the kidney may be completely asymptomatic and give no abnormal urinary findings. It may be diagnosed only by careful intravenous or retrograde pyelography. In very rare instances a primary bone tumor may pulsate. In a review of the literature, Mider and Morton [15] collected five cases of pulsating giant cell tumors. Bucy and Capp,[16] reporting on primary hemangioma of the bone, collected from the literature three cases that pulsated. Two were in the skull and one was in the clavicle. The characteristic appearances on radiography, plus the absence of a primary tumor in the kidney and thyroid, make the diagnosis of both of these bone tumors possible. In an interesting paper on pulsating tumors of the sternum, Crile [14] described nine cases arising from silent hypernephromas and nine from thyroid carcinoma. Sarcoma of the sternum or aneurysm of the aorta had been diagnosed in every case of renal carcinoma and in about one-half the cases of thyroid carcinoma. In reviewing the literature Crile was unable to find any proved case of pulsating sarcoma of the sternum. He concluded that, after ruling out an aortic aneurysm by x-ray examination, finding a pulsating mass over the sternum meant a metastasis from a renal or thyroid carcinoma.

The differentiation of a pulsating metastasis from an arterial aneurysm is usually possible on plain x-ray films of the bone involved. The osteolytic defect in the bone may not be contiguous with any major artery. However, where a

close relationship does exist, the bony defect may be interpreted erroneously to be erosion by an expanding aneurysm. In such cases angiography is capable of visualizing the normal artery and the aneurysmal nature of the bone metastasis (figure 1).

The treatment of patients with a solitary pulsating metastasis from a renal carcinoma presents the same dilemma as does a solitary nonpulsating metastasis. Nephrectomy has frequently been advised in the hope of promoting involution of the metastasis. However, as in our case, success is rarely, if ever, achieved.[1, 14, 18] Furthermore, where spontaneous involution of metastases has occurred after nephrectomy, it has been seen only with apparent but not proved metastases in the lungs.[15] In none of the cases cited by Mann [19] were the metastases in the bones. Resection of a solitary metastasis also has its advocates. In rare cases, survival of from five to 10 years has been described.[1, 14, 20] Such results must be viewed against the occasional case who survives five or more years without any surgery and the great majority who die sooner of widespread metastases. Our patient fell into the latter category. The consensus favors conservative management in the form of radiation therapy over the metastasis for the relief of pain.

Summary

Pulsating metastasis is a rare phenomenon characteristic of carcinoma of the kidney or thyroid. In the case reported, it originated from a silent hypernephroma of the left kidney. Nephrectomy did not favorably influence the metastasis. The aneurysmal nature of the metastasis was readily demonstrated by Diodrast injected into the femoral artery.

Acknowledgment

We wish to acknowledge the help of Dr. Albert M. Schwartz, who performed the Diodrast injection of the femoral artery.

Summario in Interlingua

Pulsante tumores de osso es rar. Usualmente illos representa metastases ab carcinomas renal o thyroide. Il occurre que le tumor primari es completemente asymptomatic e se discoperi solmente post un meticulose cerca. Pulsante metastases in ossos, vicin a arterias major, ha frequentemente essite misprendite pro aneurysmas. Tal errores pote esser evitate per le exacte examine radiographic del area in question. Quando il se tracta de un metastase pulsante, le radiographia revela un lesion osteolytic. Arteriographia es capace a producer un clar delineation del tumor in le osso e a demonstrar su natura aneurysmal.

Es reportate un caso. Le patiente esseva un homine de 56 annos de etate con un historia de dolores in le coxa dextere de un duration de tres menses. Un massa sensibile esseva palpabile supra le trochanter major al latere dextere. Un pulsation systolic con ruito e fremito esseva presente plus in alto. Iste signos dispareva quando le arteria femoral esseva comprimite in le triangulo femoral. Roentgenographias del coxa revelava un grande defecto osteolytic in le trochanter major e le adjacente cervice e diaphyse del femore. Nulle altere lesiones ossee esseva constatate. Nulle nodulos esseva presente in le glandula thyroide. Le urina esseva normal. Un pyelogramma intravenose exhibiva un massa al polo superior del ren al latere sinistre. Nephrectomia sinistro-lateral monstrava un clar carcinoma cellular que non invadeva le pelve, le capsula, o le venal renal. Le metastase monstrava nulle melioration post nephrectomia e radiotherapia. Metastases additional appareva. Le patiente moriva un anno post su prime symptoma de dolores coxal.

BIBLIOGRAPHY

1. Willis, R. A.: The spread of tumors in the human body, 1952, Butterworth and Co., Ltd., London.
2. Morris, H.: Pulsating tumours of the left parietal bone, associated with other similar tumours of the right clavicle and both femora and with great hypertrophy of the heart, Tr. Path. Soc. London **31**: 259, 1880.
3. Halbron, P.: Cancer thyroidien developpé au niveau du sternum et simulant un aneurysme de l'aorte, Bull. et mém. Soc. anat. de Paris **79**: 373, 1904.
4. Eshner, A. A.: Hypernephroma of the kidney with metastasis to the manubrium sterni simulating aneurysm of the aorta, J. A. M. A. **50**: 1787, 1908.
5. MacLeod, J. A., and Jacobs, W. F.: Hypernephroma of sternum, M. Rec. **100**: 979, 1921.
6. Roth, L. J., and Davidson, H. B.: Metastatic pulsating tumors of the sternum secondary to renal hypernephroma, J. Urol. **37**: 480, 1937.
7. Bullowa, J. G. M.: A case of hypernephroma with spinal metastases, M. Clin. North America **5**: 1113, 1922.
8. Rhea, L. J.: A case of metastatic thyroid tumor, Arch. Path. **2**: 293, 1926.
9. Nalle, B. C., Jr.: Distant metastases of 58 renal neoplasms; case report of secondary metastatic pulsations from renal tumor, J. Urol. **57**: 662, 1947.
10. Pool, E. H.: Bone metastasis in a case of hypernephroma, Ann. Surg. **52**: 553, 1910.
11. Scudder, C. L.: The bone metastases of hypernephroma, Ann. Surg. **52**: 533, 1910.
12. Latzko, W.: Pulsating metastasis from hypernephroma, Wien. klin. Wchnschr. **29**: 55, 1916.
13. Fabre, P., and Dambrin, P.: Tumeur pseudo-aneurysmale de la main, Ann. d'anat. path. **12**: 380, 1935.
14. Crile, G., Jr.: Pulsating tumors of the sternum, Ann. Surg. **103**: 199, 1936.
15. Mider, G. B., and Morton, J. J.: Pulsating, benign giant cell tumors of bone, Ann. Surg. **109**: 126, 1939.
16. Bucy, P. C., and Capp, C. S.: Primary hemangioma of bone, Am. J. Roentgenol. **23**: 1, 1930.
17. Lichtenstein, L.: Bone tumors, 1952, The C. V. Mosby Co., St. Louis, p. 123.
18. Lemon, H. M.: The treatment of metastatic carcinoma, M. Clin. North America **38**: 1281, 1954.
19. Mann, L. T.: Spontaneous disappearance of pulmonary metastases after nephrectomy for hypernephroma, J. Urol. **59**: 564, 1948.
20. Albrecht, P.: A study of the clinical and pathological anatomy of hypernephroma, Arch. f. klin. Chir. **76**: 1073, 1905.

SUDDEN DEATH DUE TO TRANSLUMBAR AORTOGRAPHY *

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TRANSLUMBAR aortography has received wide recognition. The introduction of water-soluble contrast media has made it relatively safe, and even high doses of dye seem usually to be well tolerated. A fatality caused by an intra-

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aortic injection of radiopaque dye is here reported. The incidence of complications in aortography will be reviewed.

Case Report

The patient, a 68 year old white male, was hospitalized in April, 1956, because of intermittent claudication in the right hip. Six months previously, following a golf match, he had experienced an acute episode of aching, nagging pain in the right hip and the posterior aspect of the right leg. The pain disappeared spontaneously, but since then he had had a walking distance of 150 steps or less. There were occasional night cramps in the right leg, but no numbness or tingling. Past history indicated diabetes mellitus for the last 18 years, for which the patient had been using 35 units of NPH insulin daily. In 1949 he experienced a myocardial infarction and spent eight weeks in bed. He had had no further anginal-type episodes. During the last six months he had become impotent.

Physical examination revealed a well developed and well nourished 68 year old white male in no acute distress. Funduscopic study evidenced no exudates or hemorrhages. The lungs were entirely clear. The heart was not enlarged, and there were no murmurs. The peripheral pulses in the upper part of the body were symmetric. The blood pressure was 130/70 mm. Hg. A faint systolic murmur was heard in the back over L1 and L2 area. The right leg showed a slight global atrophy, the right calf being one inch less in diameter than the left. There were no arterial pulses in the right lower extremity. The pulsations in the left femoral and popliteal arteries were graded as 2 plus; that in the dorsalis pedis as 1 plus. On elevation, blanching of the feet was marked in the right foot and moderate in the left. Dependent rubor on the right was 2 plus. Venous filling time was 15 seconds on both sides. There was no difference in the skin temperature of the feet. The histamine flare test showed a normal response in each leg. Oscillometric readings were 1 in the right thigh and leg and 2.75 and 2.5 in the left thigh and leg, respectively. Routine laboratory data were within normal limits.

A diagnosis of thrombosis of the common iliac artery on the right side with extension into the aorta was made and the patient scheduled for aortography. An intraocular test to sodium acetrizoate (Urokon) was negative, and an intravenous injection of 2 c.c. of the dye showed no untoward reactions.

Aortography was performed under local anesthesia. The patient received 0.2 gm. of Nembutal two hours before the procedure, and later a subcutaneous injection of 100 mg. of Demerol and 1 mg. of atropine. He was placed in the prone position on the x-ray table. Twenty cubic centimeters of 1% procaine were infiltrated into the subcutaneous tissues, deep muscle layers and around the bodies of the twelfth dorsal and first lumbar vertebrae on the left side. An 18 gauge 6 inch needle was inserted below the left twelfth rib, four inches from the midline. It reached the aorta without difficulty on the first trial. Thirty cubic centimeters of 70% Urokon were injected rapidly into the aorta, and serial exposures with a Sanchez-Perez apparatus were taken. The roentgenograms demonstrated complete obstruction of the right common iliac artery and an appositional thrombus along the wall of the lower aorta. No pain sensation was experienced during the dye injection. One minute later the patient complained of a burning sensation throughout his body. About two minutes later he became markedly dyspneic and apprehensive. His face turned blue. Urticarial lesions appeared on his forearms and shoulders. Despite immediate injection of epinephrine, he died in pulmonary edema. Heart resuscitation measures were not successful.

Autopsy revealed a small amount of blood in the para-aortic tissues in the line of the needle tract. The lungs were moderately edematous. The heart was dilated.

The coronary arteries revealed stenotic arteriosclerosis. There were numerous endocardial petechiae over the posterior aspect of the left ventricle, and a few petechiae in the epicardium. Microscopic examination revealed fibrosis of the anterior wall of the left ventricle and septum, and foci of infiltration with lymphocytes and plasma cells in the interventricular septum. The thoracic aorta was moderately sclerotic and showed a mural thrombus at the root of the innominate artery. The abdominal aorta was severely sclerotic and contained several ulcerations. The lumen of the bifurcation was almost completely filled by a soft thrombus. The right common iliac artery was occluded; the left one was stenosed in several places. Histologic examination of the aorta revealed marked atherosclerosis and medial necrosis.

Discussion

Aortography was introduced in 1929 by Dos Santos.[1] It was not very popular until 1942, at which time Nelson [2] and Doss [3] again demonstrated its advantages and reasonable safety. Its frequent use over the last 10 years has established it as an important diagnostic tool. Complications were few, and occurred only because of improper technic or injection of extreme amounts of dye.

In their anatomic studies Wagner and Price [4] pointed out that the possibility of inflicting injury upon neighboring viscera by the advancing needle is most unlikely. Mishaps may follow if the needle passes through the aorta completely or is inserted too low, at the level of the second lumbar vertebra, or too high, above the level of the twelfth thoracic. They reported entrance of the needle into the azygos system of veins. Maluf and McCoy [5] observed a complete severance of the thoracic lymph duct at the level of the tenth to eleventh thoracic vertebrae, with resulting chylothorax. A few instances of pleurisy as well as pneumothorax were also observed.[6] Shapiro [7] described injury of the splenic artery with resultant splenectomy. Joyeaux [8] observed a colocolic intussusception after use of 110% Diodrast. Deterling [9] described a severe and long-lasting chemical neuritis of the lumbar nerves as a sequela of aortography. Henline and Moore,[10] as well as Baccaglini and Ballarin,[11] demonstrated hemorrhages and inflammatory changes in the mesenteric vessels of dogs after the use of sodium iodide. Wagner and Price [4] reported a fatality they considered to have been caused by mesenteric thrombosis with gangrene of the intestine. The needle was inserted into the orifice of the superior mesenteric artery and the entire amount of 80% sodium iodide was injected into its branches. Melick and Vitt [12] described a similar event, with death occurring in 48 hours due to gangrene of the bowel, but the autopsy revealed a generalized intestinal carcinomatosis. The use of water-soluble contrast media unquestionably reduced the incidence of such disastrous effects.

Several instances of injections into the splenic, hepatic and renal arteries with only minor reactions have been reported in the literature.[6] Melick, Byrne and Bolar [13] reported intestinal necrosis in dogs from injection of sodium iodide into the superior mesenteric artery, but the organic media did not have such an effect. A grave complication of aortography is paraplegia, which so far has occurred in several cases.[14] The pathogenesis of this phenomenon is not clear. Antoni and Lindgren [15] considered the neurologic symptoms to be caused by compression of the aorta by a pillow placed under the abdomen. Hal and Skjervan [16] thought that shunts which divert the contrast material into the spinal cord circu-

lation may be responsible for this serious reaction. Evans [17] blames it on improper technic, with the needle passing through the intervertebral disc and spinal canal and enabling the dye to escape into the subarachnoid space during injection.

Systemic reactions to dye may occur immediately, as a hypersensitivity reaction, or may be delayed, due to toxic effect upon the parenchymatous organs, particularly the liver and kidneys. The iodine-containing dyes should therefore not be used in the presence of severe liver damage, poor renal function, exudative or allergic diathesis, advanced tuberculosis and sensitivity to iodides.[18] Mild iodism or hyperthyroidism is not dangerous, as the iodine is firmly bound in the modern organic contrast media.

Larson and Palmlov [19] demonstrated on 38 patients that there is ordinarily no detectable change in the renal function after aortography. A temporary diminution of function occurred only after direct injection of Diodrast into the renal arteries. Miller, Wylie and Hinman [20] reported seven instances of renal damage following aortography. These complications would probably not occur if no more than 40 c.c. of dye were injected. A case of acute renal failure leading to death has been reported by Fry,[21] who used 100 ml. of 70% Urokon in one examination. Aortography is contraindicated in patients with renal failure, as the dyes cannot be excreted promptly. This mechanism was responsible for death in the case report of Josselson and Kaplan.[22] A blood urea nitrogen of 40 mg.% is the limit above which no examination should be attempted. Toxic-allergic reactions to dye consist of nausea, vomiting, transient cyanosis and dyspnea, fall of blood pressure, feeling of heat and sudden death. Premedication does not prevent them, and drugs do not seem to help in relieving them.[14]

Pendergrass and associates [23] collected 26 instances of deaths from allergic reactions or renal damage among 661,800 examinations with radiopaque media, an incidence of 0.0039%. Cournand et al.[24] found 26 sudden deaths in a group of 6,224 patients who had had angiocardiographic examinations. So far no instance of anaphylactic reaction has been reported in instances of translumbar aortography. Our case illustrates the potential danger of fatal anaphylactic reaction. The patient developed extreme dyspnea and cyanosis and hypersensitivity reaction in the form of urticaria shortly after dye injection. The autopsy revealed pulmonary edema and a severely damaged cardiovascular system, but no adverse local reactions from the dye injection. It must therefore be assumed that the allergic reaction caused death in a person with a damaged cardiovascular system.

The sensitivity reactions cannot be absolutely prevented by previous testing and careful selection of the patients. The intradermal injection often recommended in the literature is impractical, as the highly concentrated media regularly cause skin irritations and necrosis. Of greater value is the intradermal test, with dye diluted in the patient's serum, to be read after eight and 24 hours. The intraocular route of testing may also be used, although prolonged, unpleasant irritations of the eyes occur. Two cubic centimeters of dye should be injected intravenously in the operating room and the patient observed closely for about half an hour. Cournand et al.[24] state that sensitivity to dye cannot be predicted on the basis of skin or eye tests. Reactions may occur in negative cases, whereas persons with a severe skin reaction may tolerate the procedure well. More important than all the tests is the history of allergy. Getzoff [25] recommended routine premedication with antihistamine, but the results were not very encouraging.

Stimulated by our case, we are now using cortisone routinely prior to aortography. One hundred milligrams of cortisone are given orally four hours prior to the dye injection. We have not had even a slight reaction to subsequent aortic injections. The connection with the new medication may be fortuitous, but there is adequate evidence that its use is rational as a prophylactic premedication in aortography.

Summary

Sudden death due to a hypersensitivity reaction following the intra-aortic injection of sodium acetrizoate is reported. Complications incident to aortography are reviewed. Routine use of oral cortisone as a prophylactic premedication against a dye reaction is suggested.

Summario in Interlingua

Es describite un caso de morte causate per le injection intra-aortic de un colorante radio-opac. Le patiente esseva un patiente de racia blanc de 68 annos de etate con diabete mellite qui se plangeva de claudication intermittente in le coxa dextere de sex menses de duration. Le examine physic e studios oscillometric supportava un diagnose clinic de thrombose del arteria dextero-iliac commun con extension in le aorta terminal. Esseva decidite de usar aortographia pro confirmar e delinear le diagnose. Tests de sensibilitate al colorante esseva effectuate ante le injection per medio del methodos intra-ocular e intravenose. Ambes esseva negative. Le aortographia esseva interprendite sub anesthesia local con 1% de procaina. Un punctura directe del aorta esseva effectuate sin difficultate. Trenta centimetros cubic de Urokon Natrium (acetrizoato de natrium) de 70% esseva injicite rapidemente in le aorta. Le roentgenogrammas demonstrava un obstruction complete del arteria dextero-iliac commun e un thrombo appositional al longo del pariete aortic. Un minuta post le injection del colorante le patiente se plangeva de un sensation ardente in omne partes del corpore. Duo minutas plus tarde ille deveniva dyspneic e apprehensive e disveloppava lesiones urticarial al spatulas e bracios. In despecto de un injection immediate de epinephrina e de mesuras pro le resuscitation del corde, le patiente moriva.

Le necropsia revelava un micre quantitate de sanguine in le histos para-aortic in le linea sequite per le punctura del agulia. Le pulmones esseva moderatemente edematose. Le corde esseva dilatate. Le arterias coronari revelava arteriosclerosis stenotic. Le aorta abdominal esseva severmente sclerotic e contineva plure ulcerationes. Le lumine del bifurcation esseva quasi completemente replenate per un thrombo. Le arteria dextero-iliac commun esseva occludite; le arteria sinistro-iliac commun esseva stenotic in plure sitos.

Ben que complicationes in aortographia es pauco numerose, illos pote esser variate, incluse chylothorace, pleuritis e pneumothorace, e vulneration de arterias mesenteric splenic e superior. Un grave complication es paraplegia. Reportos de morte post aortographia es summarisate.

Reactiones systemic al presentia del colorante pote occurrer immediatemente como manifestation de hypersensibilitate o tardivemente como manifestation de effectos toxic in hepate e renes. Drogas a contento de iodo non deberea esser usate in le presentia de sever damnos hepatic, de dysfunction renal, de diathese exsudative o allergic, de tuberculose avantiate, o de sensibilitate a ioduros.

Le reactiones toxico-allergic al presentia del colorante consiste de nausea, vomito, cyanosis transitori, dyspnea, hypotension, sensation de calor, e morte subitanee. Premedication non assecura lor prevention completemente. Drogas es non semper capace a alleviar los. Reactiones de sensibilitate non es completemente evitabile per previe essayos e un meticulose selection del patientes. Nos opina que le test intra-

dermal con colorante diluite in le sero del patiente mesme con observationes post octo e post 24 horas es del plus grande valor. Es proponite le uso routinari de cortisona oral como premedication prophylactic contra le possibilitate de reaction al colorante.

In tanto que le autores lo sape, isto es le prime reporto de un reaction anaphylactic mortal al presentia de colorante in aortographia translumbar.

BIBLIOGRAPHY

1. Dos Santos, R., Lamas, A. C., and Caldas, J. P.: Arteriographie des membres et de l'aorte abdominale, 1931, Masson et Cie, Paris.
2. Nelson, O. A.: Arteriography of abdominal organs by aortic injection, Surg., Gynec. and Obst. **74**: 655, 1942.
3. Doss, A. K., Thomas, H. D., and Bond, T. B.: Renal arteriography, its clinical value, Texas State J. Med. **38**: 277, 1942.
4. Wagner, F. B., Jr., and Price, A. H.: Fatality after abdominal arteriography; prevention by new modification of technique, Surgery **27**: 621, 1950.
5. Maluf, N. S. R., and McCoy, C. B.: Translumbar aortography as a diagnostic procedure in urology with notes on caval phlebography, Am. J. Roentgenol. **73**: 533, 1955.
6. McAfee, J. G., and Wilson, J. K. V.: A review of the complications of translumbar aortography, Am. J. Roentgenol. **75**: 956, 1956.
7. Shapiro, D.: Abdominal arteriography, Radiology **60**: 1, 1953.
8. Joyeaux, R. A.: Une complication abdominale grave et inedite de l'aortographie, Semaine d. hôp. Paris **26**: 152, 1950.
9. Deterling, R. H., Jr.: Direct and retrograde aortography, Surgery **31**: 88, 1952.
10. Henline, R. B., and Moore, S. W.: Renal arteriography; preliminary report of experimental study, Am. J. Surg. **32**: 222, 1936.
11. Baccaglini, G., and Ballarin, G.: Aortografia, Radiol. med. **27**: 1, 1940.
12. Melick, W. F., and Vitt, A. E.: Present status of aortography, J. Urol. **60**: 321, 1948.
13. Melick, W. F., Byrne, J. E., and Bolar, T. D.: Experimental and clinical investigation of various media used in translumbar aortography, J. Urol. **87**: 1019, 1952.
14. Koszewski, B. J., and Reedy, W. J.: Diagnostic value of translumbar aortography; a review, Circulation **16**: 120, 1957.
15. Antoni, N., and Lindgren, E.: Steno's experiment in man as complication in lumbar aortography, Acta chir. Scandinav. **98**: 230, 1949.
16. Hal, R., and Skjervan, O.: Spinal cord damage in abdominal aortography, Acta radiol. **42**: 276, 1954.
17. Evans, A. T.: Renal arteriography, Am. J. Roentgenol. **72**: 574, 1954.
18. Leriche, R., Kunlin, J., and Boely, C.: Lessons of aortography, Angiology **1**: 109, 1950.
19. Larson, H., and Palmlov, A.: Abdominal aortography with special reference to its complications, Acta radiol. **38**: 111, 1952.
20. Miller, G. M., Wylie, E. J., and Hinman, F.: Renal complication from aortography, Surgery **35**: 885, 1954.
21. Fry, W. J.: Acute renal failure and death following aortography: report of a case, Univ. Michigan M. Bull. **20**: 201, 1954.
22. Josselson, A. J., and Kaplan, J. H.: Fatal reaction following aortography with neo-iopax, J. Urol. **72**: 256, 1954.
23. Pendergrass, E. P., Chamberline, G. W., Godfrey, E. W., and Burdick, E. D.: Survey of deaths and unfavorable sequelae following administration of contrast media, Am. J. Roentgenol. **48**: 741, 1942.
24. Cournand, A., Bing, R. J., Dexter, L., Deffer, Ch., Katz, L. N., Warren, J. V., and Wood, E.: Report of committee on cardiac catheterization and angiocardiography of the American Heart Association, Circulation **7**: 769–773, 1953.
25. Getzoff, P. L.: Use of antihistamine drug prophylaxis against Diodrast reactions, J. Urol. **65**: 1139, 1951.

ERRATA

December 1957 issue, page 1119:

In figure 3 the photograph is reversed.

In the legend of figure 3 the word "right" should be changed to "left."

EDITORIAL

ENDOMETRIOSIS

THE escape of endometrial tissue from the confines of the uterus to contiguous pelvic structures results in pelvic endometriosis. This progressively incapacitating disease is characterized by its histologic resemblance to normal endometrial tissue and by a potentially invasive and malignant clinical course. The ravages of this process with involvement and perforation of hollow viscera may result in death. As a minimum, endometriosis will seriously interfere with reproductive function.

The etiology of pelvic endometriosis has long been an important point of discord among gynecologists. The proponents of the retrograde flow, metaplasia, and embryologic rest theories have defended their own concepts and denied the others bitterly throughout the years. Recent additional support of the retrograde flow concept has been gained through animal experimentation in which it has been shown that menstrual endometrium of the monkey is capable of reproducing itself. In addition, the production of pulmonary endometriosis in the rabbit and ocular endometriosis in the monkey has furthered the conjecture that pelvic endometriosis is best explained by the simple mechanical transplantation of endometrial tissue.

Epidemiologic considerations of endometriosis find it to be most common in economically favored women who have procrastinated childbearing. The average age of the patient at the onset of symptoms is 26 years. Infertility is frequently noted. These observations have prompted the gynecologic advice of early childbearing as a prophylaxis for the disease.

The symptom complex of acquired dysmenorrhea, pelvic pain, dyspareunia and painful defecation accentuated at the onset of menstrual flow, should alert the physician to a serious consideration of the diagnosis of endometriosis.

Superficial examination may reveal endometrial involvement of the umbilicus or inguinal nodes. At times there may be endometrial implants in the episiotomy, vaginal cuff scar or in an abdominal incisional scar. The most frequent finding on pelvic examination is fixed retrodisplacement of the uterus. This, in association with painful nodularity of the sacrouterine ligaments, is pathognomonic of pelvic endometriosis. Endometriosis of the rectovaginal septum may suggest neoplasia due to extreme induration. Endometriomata of the ovary will present as cystic enlargement of this structure.

It is mandatory that pelvic examination be accomplished during the early days of menstrual flow. Examination at this time will reveal extreme tenderness of the previously noted masses. The painful symptoms are due to recurrent bleeding and inflammatory change at the time of menstrual flow. This is simply a reflection of the influence of the ovarian hormones on the

aberrant tissues, even as the normally located endometrium responds to the ovarian hormonal flux.

It should be noted that all endometriosis, for some unknown reason, does not respond to the several ovarian hormones. Histologic examination, at times, will show only proliferative endometrium in some endometriosis. This will be present despite the fact that the ovarian phase may be luteal and that the endometrium in the uterus is secretory. A possible explanation for this may be found in the suggestion that there are several types of endometriosis. One as the result of retrograde menstrual flow, the others from metaplasia or embryonic rests. It is quite possible that endometriosis as the result of embryonic rests or metaplasia does not respond identically to the two ovarian hormones as does the uterine endometrium. The endometrial tissue may, on the other hand, reflect completely the presence of the circulating hormones of reproduction. Decidual change in endometriosis may be demonstrated when tissue is removed during pregnancy. It has also been shown to occur after the prolonged administration of luteoid substances.

In accordance with the physical findings and the retrograde menstrual flow hypothesis of endometriosis, the most common locations of endometriosis in the pelvis are the ovaries and sacrouterine ligaments. There is further dissemination of endometrial tissue from the endometriomata or chocolate cysts of the ovaries as recurrent shedding of these endometrial sites occur. The finding of endometrial tissue in the rectovaginal septum is also common. Less common sites in the pelvis include the cervix, vagina and vulva. Involvement of the inguinal lymph nodes and umbilicus occur with less frequency. Fortunately, invasion of the rectum and bladder to the point of perforation does not occur with any great frequency. Involvement of the rectum from endometriosis of the uterus and sacrouterine ligament is a common cause of perforation of the bowel during pelvic surgery.

Since the symptoms and progression of the disease process are necessarily dependent upon ovarian function and particularly related to ovulatory menstrual bleeding, it follows that castration must be the ultimate cure for the disease. This cessation of ovarian function may be the result of surgery, irradiation or the climacteric. The consequential associations of the positive act of castration are such that other more conservative means of therapy have been sought.

The most satisfactory non-surgical therapy of endometriosis is pregnancy. This should be accomplished for several reasons. The prophylactic possibilities of pregnancy have already been mentioned. The progression of the disease suggests that if the patient desires children her chances for pregnancy can never be greater than the present. There is also much to indicate that even in well established endometriosis there is a dramatic remission of symptoms during gestation. In addition, this symptomatic relief may persist for months or years following the termination preg-

nancy. Because of these observations, the consensus of gynecologic opinion is that the primary initial treatment of pelvic endometriosis should be pregnancy.

Since many of these patients are infertile, the establishment of pregnancy may be difficult. Even in a married woman who earnestly desires pregnancy and in whom there are no contraindications for pregnancy, the gravid state may be difficult to attain. The exact reason for infertility in these patients with endometriosis is far from explained. The majority have satisfactory ovarian function with demonstrable ovulation. Most have patent oviducts. However, even when these conditions are present and union with an apparently fertile male has been obtained, pregnancy is frequently impossible to achieve.

The explanations for the efficacy of pregnancy in providing temporary relief for the patient with endometriosis are not entirely satisfactory. It is quite possible that simply the prevention of cyclic bleeding in endometrial implants may provide a remission of symptoms.

When pregnancy cannot be achieved in the young woman with endometriosis, utilization of an hormonal pregnancy equivalent will often provide symptomatic relief similar to that achieved by pregnancy. The pregnancy equivalent may be obtained through a systematic program of estrogen administration. In this regimen, stilbestrol is administered orally in gradually increasing doses to a total of 100 milligrams a day. The estrogen is continued at this maximum dosage level for about six months. During this period the patient is anovulatory. The reproductive tract undergoes those changes similar to pregnancy which are the result of circulating estrogen. These include uterine enlargement, softening of the cervix and bluish discoloration of the vagina and cervix. In addition, the breasts become turgid, enlarged and the areola darkly pigmented.

During the administration of stilbestrol, all patients are symptom-free. As in pregnancy, this relief of symptoms may persist from months to years following the discontinuation of therapy. Recently, the addition of luteoid substances to the regimen, thereby more closely simulating the hormonal pattern in pregnancy, has been suggested. Whether the additional hormone will increase the effectiveness of this type of therapy has not been shown.

Conservative surgery is the next step in the treatment of the patient with pelvic endometriosis. Should pregnancy not be advisable or not obtainable and a trial of pregnancy substitute unsatisfactory, then surgery should be attempted. The first surgical attempt should be conservative, in which accessible endometrial implants are removed. It is idiomatic in the treatment of endometriosis by surgery that each patient will often require two indicated operations; the first one conservative and if symptomatic relief is not obtained, this may conscientiously be followed by radical pelvic surgery accompanied by bilateral oophorectomy.

Pelvic endometriosis offers many challenges to the physician and ex-

perimenter. It is an important link clinically between benign and malignant neoplasia. The etiologic aspects of the disease, particularly as it relates to early childbearing, is an important consideration for the sociologist as well as the gynecologist. Metaplasia and embryonic rests as causes of endometriosis are important to the embryologist and pathologist. The gynecologist may play an important role in the prevention of endometriosis by recommending early childbearing. He may also prevent the dissemination of menstrual endometrium by not performing retrograde studies of the oviducts at or about the time of menstrual flow. The gynecologic-endocrinologist finds much of importance in an experimental and therapeutic nature in the treatment of pelvic endometriosis. The substitution of a pregnancy equivalent for pregnancy provides a fertile ground for studying the effects of massive doses of estrogen and progesterone in the non-pregnant patient. Surgery in the treatment of endometriosis is a real test for the operator. The conservative approach by the pelvic surgeon is an extremely provocative one in the demands upon his technic and his surgical judgment. Unfortunately, these problems, although interesting and challenging to the physician, have categorized endometriosis as a serious and oftentimes a disabling disease in the young woman of the higher social and economic groups. It can be only through the combined efforts of the entire medical and related disciplines that this problem will ultimately reach its proper resolution.

ARTHUR L. HASKINS, M.D.

REVIEWS

Bronchopulmonary Diseases: Basic Aspects, Diagnosis and Treatment. Edited by EMIL A. NACLERIO, M.D. 956 pages; 20.5 × 28 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1957. Price, $24.00.

The authors of this large volume have provided the non-specialist with broad and sound principles for a clear understanding of diseases of the tracheobronchial tree and the lung. More precise diagnostic methods, improved thoracic surgery technics, the production of antimicrobial drugs, and increased knowledge of respiratory physiology all have been associated with a great increase in interest and productivity in this field.

Problems of bronchopulmonary disease are faced by all physicians and surgeons. The book contains a great deal of useful, well presented material which will enable the doctor to approach such patients intelligently.

The initial sections deal with developmental defects, segmental bronchopulmonary anatomy, and normal respiratory physiology. Alterations of pulmonary function in disease states are discussed. There is a lucid presentation of current concepts of pathogenesis of various disease states. Diagnostic technics, including various radiographic methods, receive extensive consideration. Some of the cardiovascular diseases caused by or resulting in pulmonary abnormalities are analyzed. Considerable space is given to the problem of tumors, benign and malignant, primary or metastatic. Clear and concise sections deal with tuberculous and mycotic infections and with pulmonary sarcoidosis. Pulmonary emphysema, an ever-increasing medical and socioeconomic problem, is the subject of several chapters. Various aspects of thoracic surgery and associated problems of anesthesia are discussed. The restraint exhibited by the editor, a surgeon, in limiting technical material pertaining to operative procedures is commendable.

Compiling a book of this comprehensive scope is an enormous task. Obviously all 142 authors are not equally facile writers, and a certain unevenness occurs in the presentations. Any first edition is bound to have occasional errors, a lack of cohesiveness, some contradictions and redundancies. Along this line one must question the need for three essays on "coin" lesions and two articles discussing plastic surgery procedures on the airways. On pages 776 and 777, $CrP^{32}O_4$ is incorrectly designated radioactive colloidal "chronic" phosphate in the captions for illustrations, although the correct term (chromic) appears in the text. The EKG on page 219, figure 3B, is a more characteristic example of right ventricular hypertrophy than the one on page 198. In future editions it is hoped that some of the radiographs will be more clearly reproduced and precisely labeled.

Differences of opinion exist concerning many aspects of bronchopulmonary disease, and certain recommendations in the text must be questioned. Pneumoperitoneum and autonomic surgery in the treatment of chronic pulmonary emphysema, not widely accepted by specialists in this field, have prominent space allotted to them. No critical evaluation of these technics is offered in the text. Again, frequent phlebotomy and long-term use of antibiotic drugs in the management of chronic emphysema are not, in the opinion of the reviewer, universally valuable or indicated measures. Finally, the development of thoracic surgery to its present high state has made exploratory thoracotomy a safe procedure with insignificant morbidity or mortality risks. Therefore, one must unequivocally object to needle biopsy of the lung (page 79) or a therapeutic dose of x-ray (page 80) as useful procedures in the diagnosis of endothoracic disease. When one is unsure of the diagnosis, a tissue biopsy at thoracotomy is essential for histologic and bacteriologic study. Needle biopsy is risky and unwarranted, since it may cause extension of a tumor, spread of

infection, pneumothorax or empyema, and does not invariably produce a piece of tissue satisfactory for study.

Dr. Naclerio, his collaborators, and the publishers are to be complimented for producing a readable, instructive, valuable book. It should be available as a reference work for use by medical students, house officers, and physicians and surgeons. Most of the sections have good bibliographies, and the material is well indexed.

JEROME E. COHN, M.D.

Clinical Physiology: The Functional Pathology of Disease. Edited by ARTHUR GROLLMAN, M.D., Ph.D., F.A.C.P., Professor and Chairman of the Department of Experimental Medicine, University of Texas Southwestern Medical School, Dallas. 854 pages; 16 × 24 cm. The Blakiston Division, McGraw-Hill Book Co., Inc., New York. 1957. Price, $12.50.

Clinical Physiology or Pathophysiology or Applied Physiology (whatever the name—so long as Physiology is, to quote from Dr. Grollman's preface, "used in the spirit in which Claude Bernard defined it, as 'the experimental basis of medicine' ") has become a popular subject for books; and rightly so. Medicine is progressing rapidly because of experimentation, and many of us need summarization in fields which we cannot follow with discrimination by reading journal articles.

Each such book on the market is good; this one is especially good. It has several sections that, to my mind, have everything needed by a good review article—authority (which implies being current), lucidity (readable), comprehensiveness (without undue emphasis on the author's research) and with critically selected references. The same can be said of other available books; fortunately, the outstanding parts of one book complement the weak points of another.

It may be unfair to name names, but one wonders how the Nobel Laureates—Cournand and Richards—found time and energy to write 70 masterful pages about the respiratory system in health and disease. The late John P. Peters did equally well with carbohydrate, protein and lipid metabolism. Dr. William B. Bean has the background and ability to present those aspects of vitamins that are really needed by a clinician without the usual dross.

The book has many other excellent chapters; in fact, it has but two that might well have been omitted. Also, certain subjects cannot be presented in a chapter whose length must be limited. Except for this—asking one or two authors to put a large subject into a small chapter and including works of an authority that are not authoritative—Dr. Grollman has expertly edited a fine and useful book. In fact, it is stated in the preface that some contributors felt that the editing was too vigorous. In editing, to be expert requires vigor.

Despite the kudos, something is lacking. *The* book on Clinical Physiology has not yet been written; it probably will not be written by a group of authors who are geographically separated. Yet, it is not impossible. About 15 years ago, two men wrote a book on Pharmacology that also *covered the field* of Clinical Physiology better than has been done since. It had few sections better than the best in this book; but because of the unified view presented, it has not yet been matched.

B. W. A.

Shock and Circulatory Homeostasis: Transactions of the Fourth Conference, December 6, 7, and 8, 1954, Princeton, N. J. Edited by HAROLD D. GREEN, M.D. 291 pages; 16 × 23.5 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. 1955. Price, $5.00.

This monograph reports the transactions of the Fourth (1954) Josiah Macy sponsored conference on Shock and Circulatory Homeostasis. Emphasized are the circulatory dynamics in the normal and "shock" state of the peripheral, splanchnic,

pulmonary and coronary beds. The effect of epinephrine on respiration and the central nervous system also receives consideration. Plethysmography, the thermoelectric needle and polarographic determination of skin oxygen tension receive detailed comment as methods of study of the peripheral circulation. They are compared with the radioactive sodium clearance method. The arteriovenous muscle shunt is offered as an explanation for discrepancies occurring among the methods. The debate on hepatic vein and pulmonary artery wedge pressures should be of interest to the vascular surgeon. The accuracy of the Fick principle, effect of anoxia on pulmonary circulation, and changes in coronary flow during the cardiac cycle are described.

These documented discussions provide an opportunity for a comprehensive review of contemporary research on circulatory dynamics. Their greatest appeal will be to the clinician and physiologist interested in circulatory responses in the human body. As a bonus, there is an introduction by Dr. Fremont-Smith explaining the philosophy of "group conference programing," a practice currently in vogue.

F. J. B.

Atlas of Tumors of the Nervous System. By H. M. ZIMMERMAN, M.D., MARTIN G. NETSKY, M.D., and LEO M. DAVIDOFF, M.D. 191 pages; 20 × 27.5 cm. Lea & Febiger, Philadelphia. 1956. Price, $25.00.

This atlas is inclusive in scope and presents a traditional approach to the problem of neural tumors. A severely restricted text is clearly written but does not refer closely to the illustrations. The old problem of semantics creeps into this atlas in that it does not closely follow any of the proposed classifications and contains some conflicting terminology. The classification offered by the authors is not supported in the text.

An appendix relating to staining technics is incomplete and is without comment as to the reason for choosing the specific stains. There is no stated relationship between this appendix and the stains employed in the illustrations, although this is inferred. An attached incomplete bibliography bears no relationship to the text and illustrations.

It is obvious that the prime purpose of this volume is to display typical illustrations of neural tumors. However, due to either poor photography or poor reproduction, many of the illustrations are of such quality that they cannot be identified with certainty even through the use of the captions. Some are poorly chosen. Some artist drawings are pleasant but do not accomplish anything that a photograph could not have shown. In fact, several drawings could be replaced by photographs with improvement. Figures cited and numbered do not refer to the text and therefore serve no useful purpose. While it is true that there are "non-neoplastic tumors," general usage of the word tumor customarily indicates neoplasm. The atlas includes some non-neoplastic conditions such as aneurysm, gumma, parasitic cysts, tuberculoma and abscess. There is, however, no reference to other expansile lesions such as intracerebral hematomas. The reason for the inclusion of neoplasms of the skull is not clearly stated.

There are many good photomicrographs and gross illustrations. With revisions of certain features, this atlas in a second edition should prove a very useful volume.

J. A. W.

Martius' Gynecological Operations, with Emphasis on Topographic Anatomy. Translated and Edited by MILTON L. MCCALL, M.D., F.A.C.S., and KARL A. BOLTEN, M.D. 405 pages; 18.5 × 26.5 cm. Little, Brown and Company, Boston. 1957. Price, $20.00.

This classic work of an eminently qualified German gynecologist was originally published in 1936 and translated into English for the first time in 1939. The seventh

and last German edition appeared in 1954. This book represents a translation of the last edition.

The reason for its wide European acceptance immediately becomes apparent on perusal. Logical continuity and lucid brevity without oversimplification of the descriptive text directly complement numerous vivid illustrations, most of which are in color. Diagrammatic anatomic sketches and operative procedure have been purposefully arranged together so as to facilitate correlation. Pelvic topography and surgical technic are comprehensively and precisely detailed. The clarity of the drawings and labels transmits an uncluttered perspective to the observer. This feature is all too commonly lacking in the average manual of this type.

Procedures not generally practiced in the United States such as subtotal vaginal hysterectomy, vaginal tubal sterilization with fixation of the tubal knuckle extraperitoneally, exohysteropexy for vaginal prolapse, and subtotal colpoperineocleisis are discussed and demonstrated. The sections on vaginal operations and urinary incontinence deserve specific mention for their completeness and precision.

Although the Wertheim hysterectomy technic is completely considered, reference to other more radical pelvic exenterations, as practiced in Holland and Germany, is noticeably lacking. Increasing interest by the American surgeon in the surgical treatment of radio-resistant genital cancer imposes a need for the inclusion of these radical methods.

The table of contents and the index have been thoughtfully planned for the convenience of both the avid or occasional reader. The paper is heavy and of fine quality. The type is striking. The translation of a foreign book is a laborious task in itself, but the conveyance of an author's original subjectivity is a genuine literary accomplishment. In both respects the editors have succeeded commendably. This volume should find a niche on the shelves of every gynecologist.

E. D. N.

The Office Assistant in Medical or Dental Practice. By PORTIA M. FREDERICK and CAROL TOWNER. 351 pages; 15 × 21 cm. W. B. Saunders Co., Philadelphia. 1956. Price, $4.75.

The Office Assistant is an excellent reference book pertaining to a variety of subjects including those of receptionist, typist, nurse, bookkeeper and housekeeper, which will help the medical secretary in her work. It provides information of great assistance to the individual who is called upon to perform the many duties in a doctor's office. The presentation of this material is painstakingly detailed though obviously the text has a limited market.

E. G. S.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Adventures in Medical Education: A Personal Narrative of the Great Advance of American Medicine. By G. CANBY ROBINSON, M.D., LL.D., Sc.D. 338 pages; 23.5 × 16 cm. 1957. Published for The Commonwealth Fund by Harvard University Press, Cambridge. Price, $5.00.

The Bacteriology of Tuberculosis. By EGONS DARZINS, M.D., Research Scientist, Anoka State Hospital. 488 pages; 24 × 16 cm. 1958. University of Minnesota Press, Minneapolis. Price, $10.00.

Bilateral Polycystic Disease of the Kidneys: A Follow-Up of Two Hundred and Eighty-four Patients and Their Families. By O. Z. DALGAARD. 255 pages; 24 × 17.5 cm. (paper-bound). 1957. Ejnar Munksgaard, Copenhagen.

Das Bluteiweissbild. By PROF. DR. ROLF EMMRICH. 227 pages; 24.5 × 16.5 cm. 1957. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 37.–; Ganzleinen DM 40.—.

Comparative Aspects of Haemolytic Disease of the Newborn. By G. FULTON ROBERTS, M.A., M.D., Fellow of Jesus College, Cambridge, and Lecturer in Pathology in the University. 199 pages; 19 × 12.5 cm. 1957. Grune & Stratton, Inc., New York. Price, $3.00.

Drug Resistance in Micro-organisms: Mechanisms of Development. Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and CECILIA M. O'CONNOR, B.Sc. 352 pages; 21 × 14.5 cm. 1957. Little, Brown and Company, Boston. Price, $9.00.

Drugs: Their Nature, Action and Use. By HARRY BECKMAN, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, etc. 728 pages; 26 × 18 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $15.00.

Etude de la fonction thyroidienne avec l'iode radioactif. By PROF. DR. A. VANNOTTI. 203 pages; 24 × 16 cm. (paper-bound). 1957. Benno Schwabe & Co., Basel; available in U. S. A. from Intercontinental Medical Book Corporation, New York. Price, $6.25.

Forensic Medicine: A Text-book for Students and a Guide for the Practitioner. 6th Ed. By DOUGLAS J. A. KERR, M.D., D.P.H., F.R.C.P. (Edin.), F.R.S. (Edin.), Regius Professor of Forensic Medicine in the University of Edinburgh. 363 pages; 22.5 × 14 cm. 1957. The Macmillan Company, New York. Price, $6.50.

Fundamentals of Electrocardiography and Vectorcardiography. By LAWRENCE E. LAMB, M.D., Director of Cardiology and Chief, Department of Internal Medicine, Air University, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas, etc. 142 pages; 28.5 × 22 cm. 1957. Charles C Thomas, Publisher, Springfield, Illinois. Price, $9.50.

General Diagnosis and Therapy of Skin Diseases: An Introduction to Dermatology for Students and Physicians. By HERMANN WERNER SIEMENS, M.D., Professor of Skin and Venereal Diseases at the University of Leiden, Holland; translated from the German edition by KURT WIENER, M.D., Dermatologist, Mount Sinai Hospital, St. Michael Hospital, Evangelical Deaconess Hospital, Milwaukee, Wisconsin. 324 pages; 24.5 × 17.5 cm. 1958. The University of Chicago Press, Chicago. Price, $10.00.

An Introduction to Medical Mycology. 4th Ed. By GEORGE M. LEWIS, M.D., Professor of Clinical Medicine (Dermatology), Cornell University Medical College, etc.; MARY E. HOPPER, M.S., Research Fellow in Medicine, Cornell University Medical College; J. WALTER WILSON, M.D., Clinical Professor of Medicine, University of Southern California, etc.; and ORDA A. PLUNKETT, Ph.D., Professor of Botany, University of California at Los Angeles, etc. 453 pages; 26 × 18 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $15.00.

The Neuroses and Their Treatment. Edited by EDWARD PODOLSKY, M.D., F.A.P.A., F.A.P.M., Department of Psychiatry, Kings County Hospital, Brooklyn, New

York, etc. 555 pages; 21.5 × 14.5 cm. 1958. Philosophical Library, New York. Price, $10.00.

The Peter T. Bohan Memorial Lectures on Medicine. First Series. By RUSSELL L. HADEN, M.D., WALTER CLEMENT ALVAREZ, M.D., JOHN T. KING, M.D., HERMAN L. KRETSCHMER, M.D., D.Sc., CLAUDE FRANK DIXON, M.D., PAUL D. WHITE, M.D., and ROY W. SCOTT, M.D. 128 pages; 24.5 × 16.5 cm. 1957. University of Kansas Press, Lawrence. Price, $3.00.

The Pharmacologic Principles of Medical Practice: A Textbook on Pharmacology and Therapeutics for Medical Students, Physicians, and the Members of the Professions Allied to Medicine. 4th Ed. By JOHN C. KRANTZ, JR., Professor of Pharmacology, School of Medicine, University of Maryland, etc.; and C. JELLEFF CARR, Senior Research Pharmacologist, Psychopharmacology Service Center, National Institute of Mental Health etc. 1,313 pages; 23.5 × 15.5 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $14.00.

Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine and Its Allied Professions. 3d Ed. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P., Lecturer in Pharmacology and Toxicology, The Medical Branch, and Professor and Chairman of the Department of Experimental Medicine, The Southwestern Medical School, The University of Texas, etc. 1,034 pages; 24 × 15.5 cm. 1958. Lea & Febiger, Philadelphia. Price, $12.50.

Physical Methods in Physiology. By W. T. CATTON, M.Sc., Physiology Department, King's College, Newcastle-upon-Tyne. 375 pages; 19.5 × 12.5 cm. 1957. Philosophical Library, New York. Price, $10.00.

Prisma. By GUILLERMO TRUJILLO DURÁN. 303 pages; 24 × 16.5 cm. (paper-bound). 1957. Publicación de la Universidad Nacional del Zulia, Dirección de Cultura, Caracaibo, Venezuela.

Psychiatry and the Criminal: A Guide to Psychiatric Examinations for the Criminal Courts. By JOHN M. MACDONALD, M.D., Assistant Professor of Psychiatry, University of Colorado School of Medicine, etc. 227 pages; 23.5 × 16 cm. 1958. Charles C Thomas, Publisher, Springfield, Illinois. Price, $5.50.

Recent Advances in Urology. By HOWARD G. HANLEY, M.D., F.R.C.S., Surgeon, St. Peter's, St. Paul's and St. Philip's Hospitals, etc., with the assistance of specialist contributors. 270 pages; 21 × 13.5 cm. 1957. Little, Brown and Company, Boston. Price, $7.00.

Taschenbuch der Herz- und Kreislauftherapie. By PROF. DR. MED. DR. h. c. H. W. KNIPPING and DR. MED. H. LOOSEN. 234 pages; 21.5 × 15 cm. 1957. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 20.60; Ganzleinen DM 24.–.

Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. Band 23: Kreislauf in Narkose und Hypothermie—Angeborene Herzfehler. Herausgegeben von PROF. DR. RUDOLF THAUER. 416 pages; 23 × 15.5 cm. (paper-bound). 1957. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 54,–.

Le Volume Sanguin des Poumons chez l'Homme. By JACQUES LAMMERANT. 192 pages; 24 × 16 cm. (paper-bound). 1957. Éditions Arscia, Brussels. Price, Frs. Belges 180,—.